St.Lideta Health Science and Business College

Department of Pharmacy

Fundamental Organic Chemistry

CHAPTER 4

Major Organic Reactions

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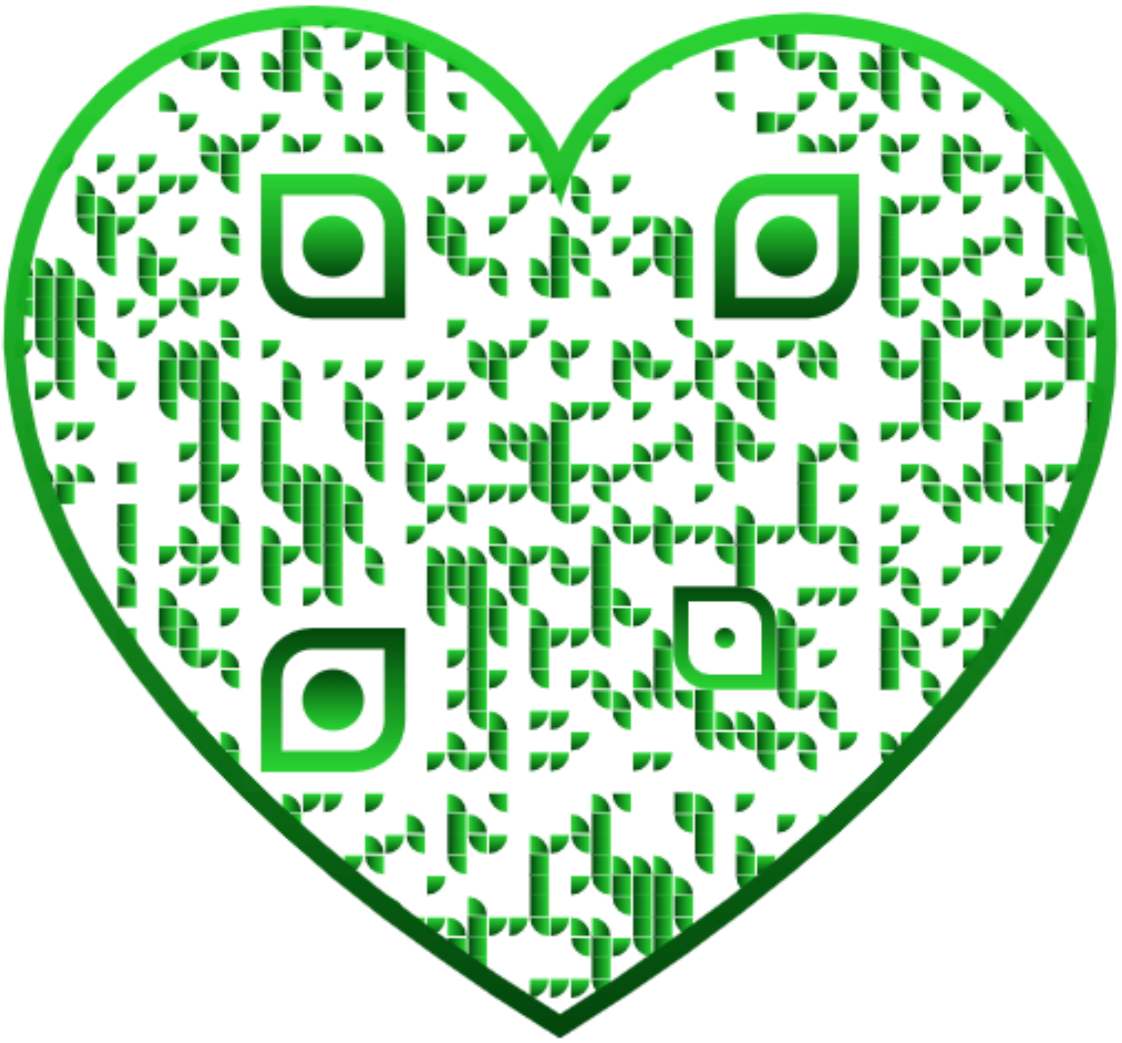


Introduction

- **An organic reaction is a change in structure or functional group leading to formation of a new substance.**
- **The undergoing a change in structure or functional group is compound called a reactant or substrate.**

Alkyl halide **alcohol**

Reactant **product**

- **All chemical reactions involve bond-breaking in the reactant molecules and bond-making in the product molecules.**
- **Fundamentally, a covalent two electron bond can break in two ways:**
  - **Homolytic cleavage**
  - **Heterolytic cleavage**

- **Homolytic cleavage** a bond can break in an electronically *symmetrical* way so that one **electron remains with each product fragment .**

Bonding electron stays with each product.

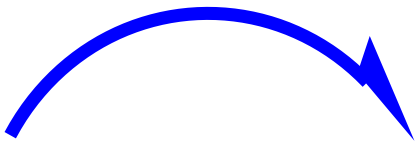
- **Heterolytic cleavage** a bond can break in an electronically *unsymmetrical* way so that **both electrons remain with one product fragment**, leaving the other fragment with a vacant orbital.

two bonding electrons stay with one product.

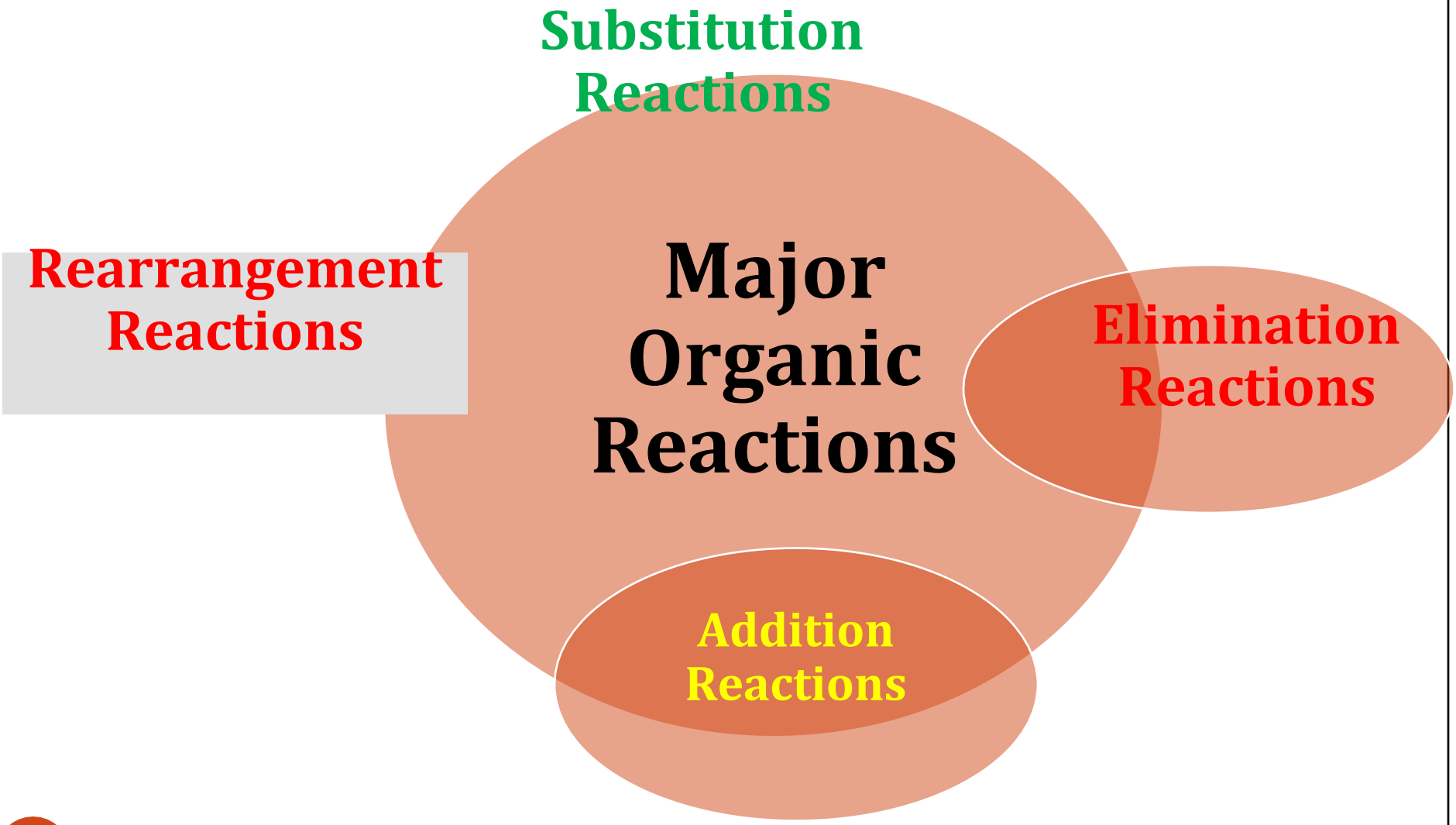
Reaction Mechanism

- **The description of the step-by-step process by which reactants are changed into products.**
- **An overall description of how a reaction occurs.**
- **A mechanism describes:**
  - **which bonds are broken and in what order**
  - **which bonds are formed and in what order and**
  - **what the relative rates of the steps.**

An arrow head with two barbs signifies the movement of two electrons.



An arrow head with one barb signifies the movement of one electron


Substitution Reactions
Rearrangement Reactions
Major Organic Reactions
Elimination Reactions
Addition Reactions

1. Substitution Reactions

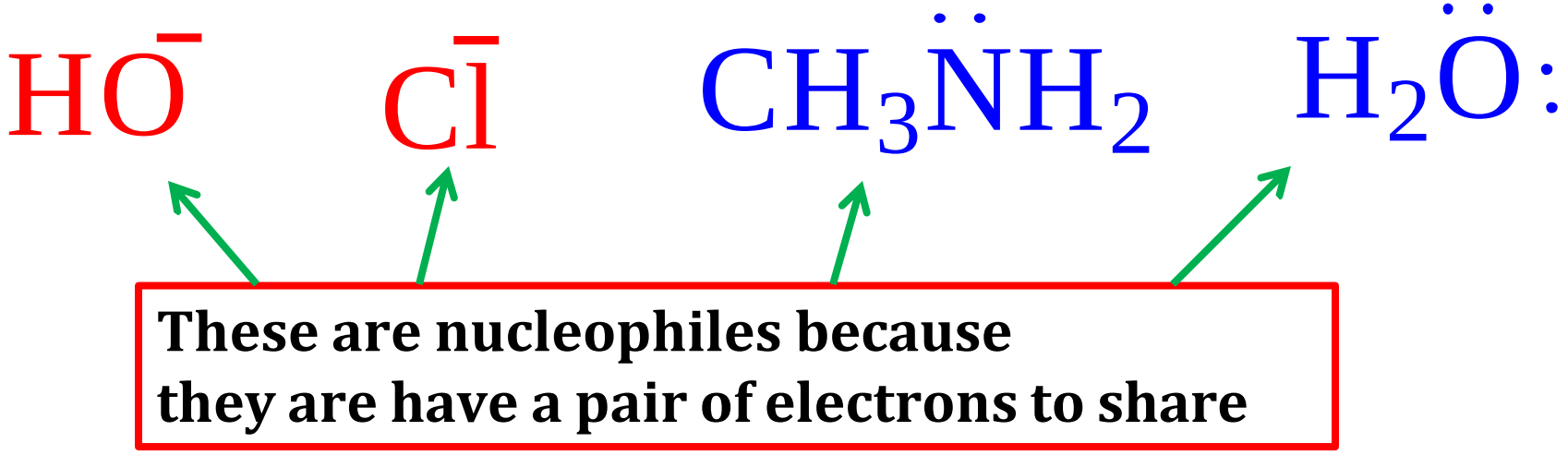
- **Substitution reaction, the electronegative atom or group is replaced by another atom or group.**

- **The atom or group that is substituted or eliminated in these reactions is called a leaving group.**
- **An electron-deficient atom or molecule is called an electrophile.**
- H^+ $CH_3\overset{+}{C}H_2$ BH_3 Br

These are electrophiles because they can accept a pair of eletron

This is an electrophile because It is seeking of an electron

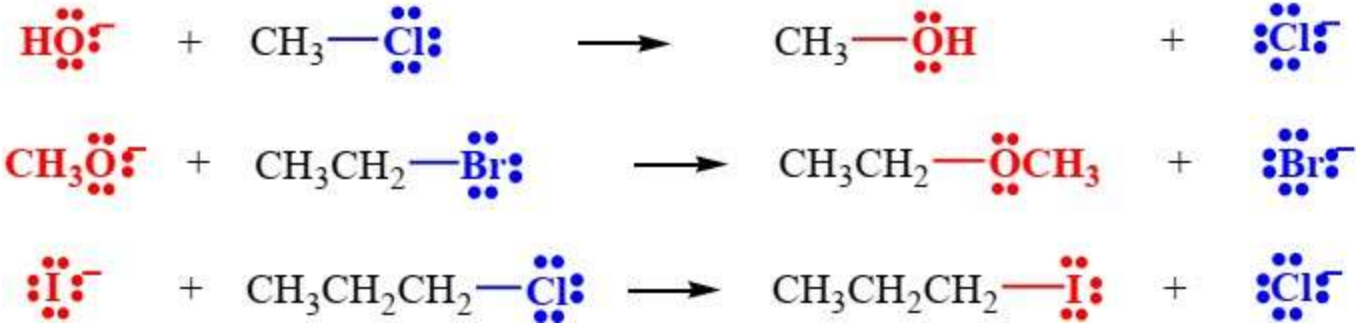
- **An electron-rich atom or molecule is called a nucleophile.**
- **A nucleophile has a pair of electrons it can share.**
- **Some nucleophiles are neutral and some are negatively charged.**



Nucleophilic Substitution Reactions

Nucleophile **Alkyl halide (substrate)** **Product** **Halide ion**

***Examples*:**



- **There are two important mechanisms for the nucleophilic substitution reaction.**

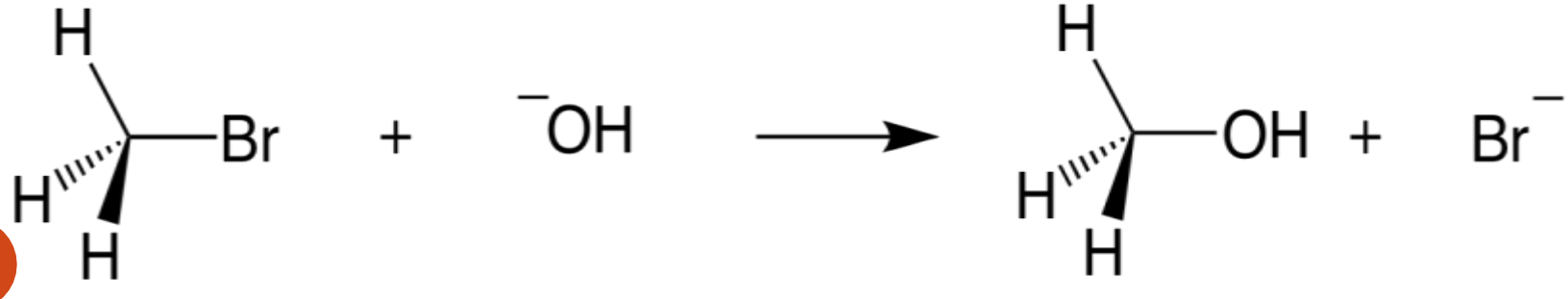
1. **S_N2, Nucleophilic substitution bimolecular**
2. **S_N1, Nucleophilic Substitution unimolecular**

S_N2, Nucleophilic substitution bimolecular

- **Bimolecular (or 2nd order) means that the rate of an S_N2 reaction depends on the concentrations of *two* substances (alkyl halide and nucleophile).**

$$\text{Rate} = k\,[RX]\,[Nu:^-]$$

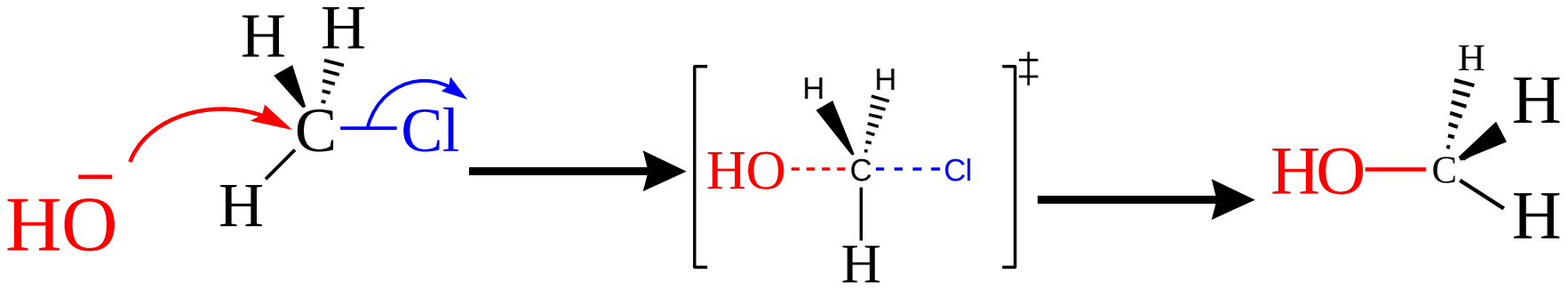
- **If the concentration of alkyl halide doubled, the rate reaction also doubles.**
- **If the concentration of nucleophile is doubled, the rate of the reaction also doubles.**
- **If the concentrations of both reactants are doubled, the rate of the reaction quadruples.**



- **Reaction**

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^-$$

- **Mechanism**



✓**hydroxide ion pushes a pair of electrons into the partially positive carbon from the back side.**

- **chlorine begins to move away**

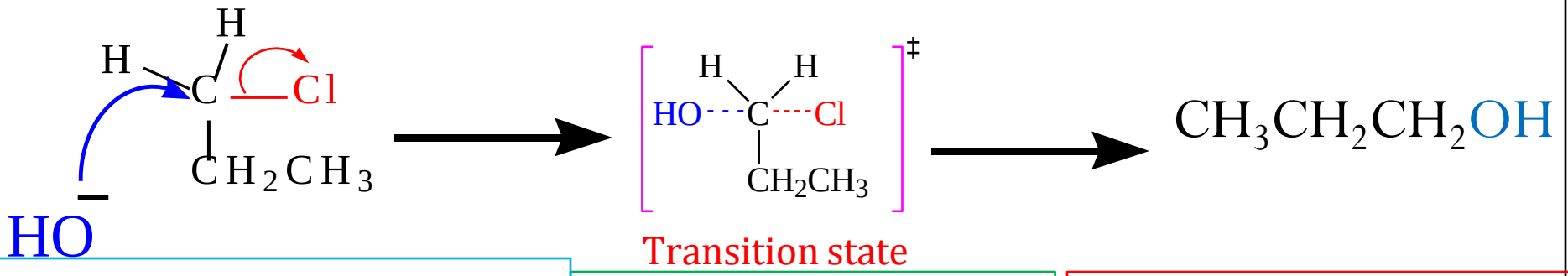
Transtion state

A bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken.

carbon- oxygen bond formed and the chloride has departed.

1. **What is the substitution product from reaction of 1-chloropropane with NaOH?**

$CH_3CH_2CH_2Cl + {}^-OH$ S_N2 ⟶



Transition state

The Nu^- approach to partially positive charged carbon

Partially bond forming and breaking

C- O bond formed and the chloride departed.

- **S_N2 reaction**

- **SN2 reaction is Concerted reaction**
  - **so no intermediates are formed and one step reaction**
- **Undergo back-side attack.**
  - **The nucleophile hits the carbon on the side opposite the side bonded to the leaving group.**

Factors Affecting Rate of S_N2 Reactions

1. The nature of the substrate

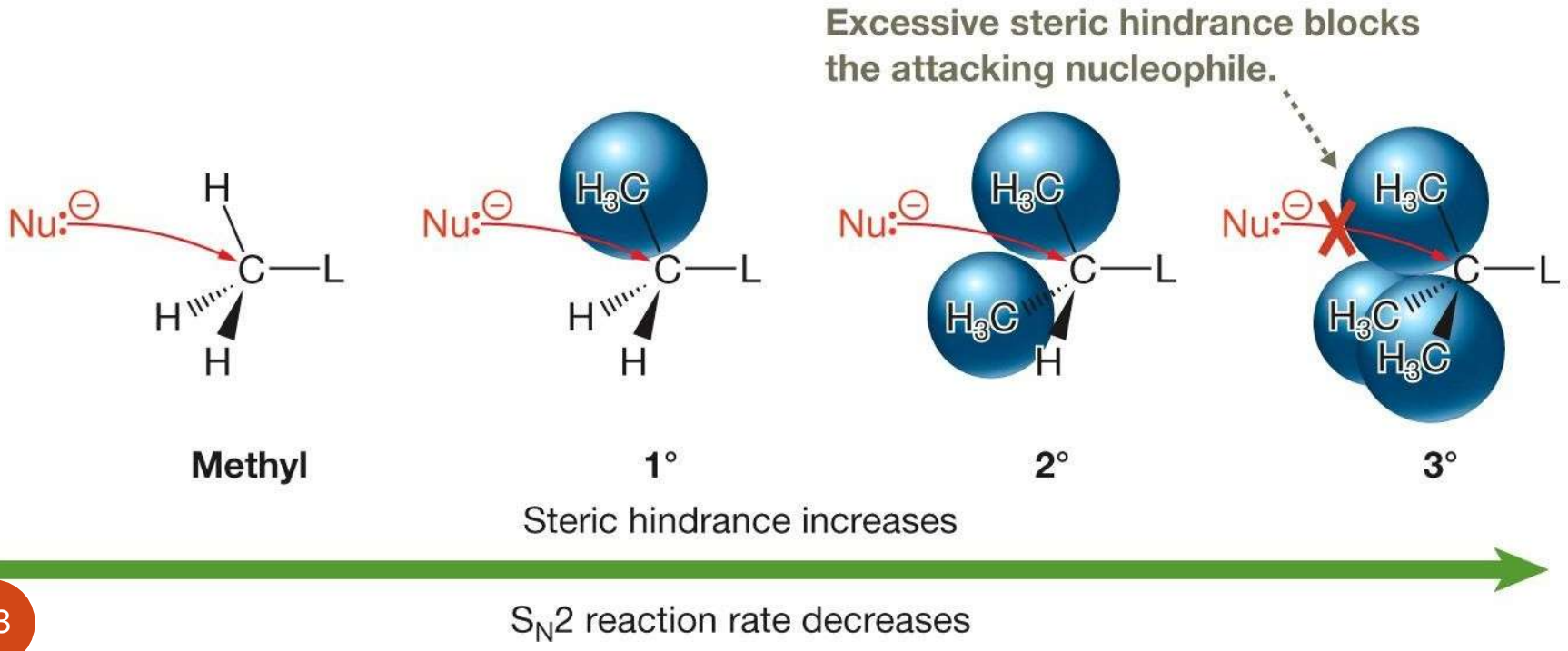
Me° >> 1° >> 2° >>3°

$$R{-}Br + Cl^- \xrightarrow{S_N2} R{-}Cl + Br^-$$

Alkyl halide	Class of alkyl halide	Relative rate
$CH_3{-}Br$	methyl	1200
$CH_3CH_2{-}Br$	primary	40
$CH_3CH_2CH_2{-}Br$	primary	16
$CH_3CH(CH_3){-}Br$	secondary	1
$CH_3C(CH_3)_2{-}Br$	tertiary	too slow to measure

Steric effects are caused by groups occupying a certain volume of space. A steric effect that decreases reactivity is called steric hindrance.

- **Methyl halides reacts quickly in S_N2 reactions, but a 3° does not react.**
- **The back side of an α-carbon in a 3° alkyl halide is completely blocked.**
- **Tertiary alkyl halides cannot undergo S_N2 reaction.**



2. The nature of Leaving Group

	relative rates of reaction
$HO^- + RCH_2I \longrightarrow RCH_2OH + I^-$	30,000
$HO^- + RCH_2Br \longrightarrow RCH_2OH + Br^-$	10,000
$HO^- + RCH_2Cl \longrightarrow RCH_2OH + Cl^-$	200
$HO^- + RCH_2F \longrightarrow RCH_2OH + F^-$	1

- **Iodide ion is the best leaving group and the fluoride ion is the worst**
- **Alkyl iodides are the most reactive of the alkyl halides and alkyl fluorides are the least reactive.**
- **Alkyl fluorides do not undergo S_N2 reactions**

RI > RBr > RCl > RF

most reactive

least reactive

3. The nature of the Nucleophile

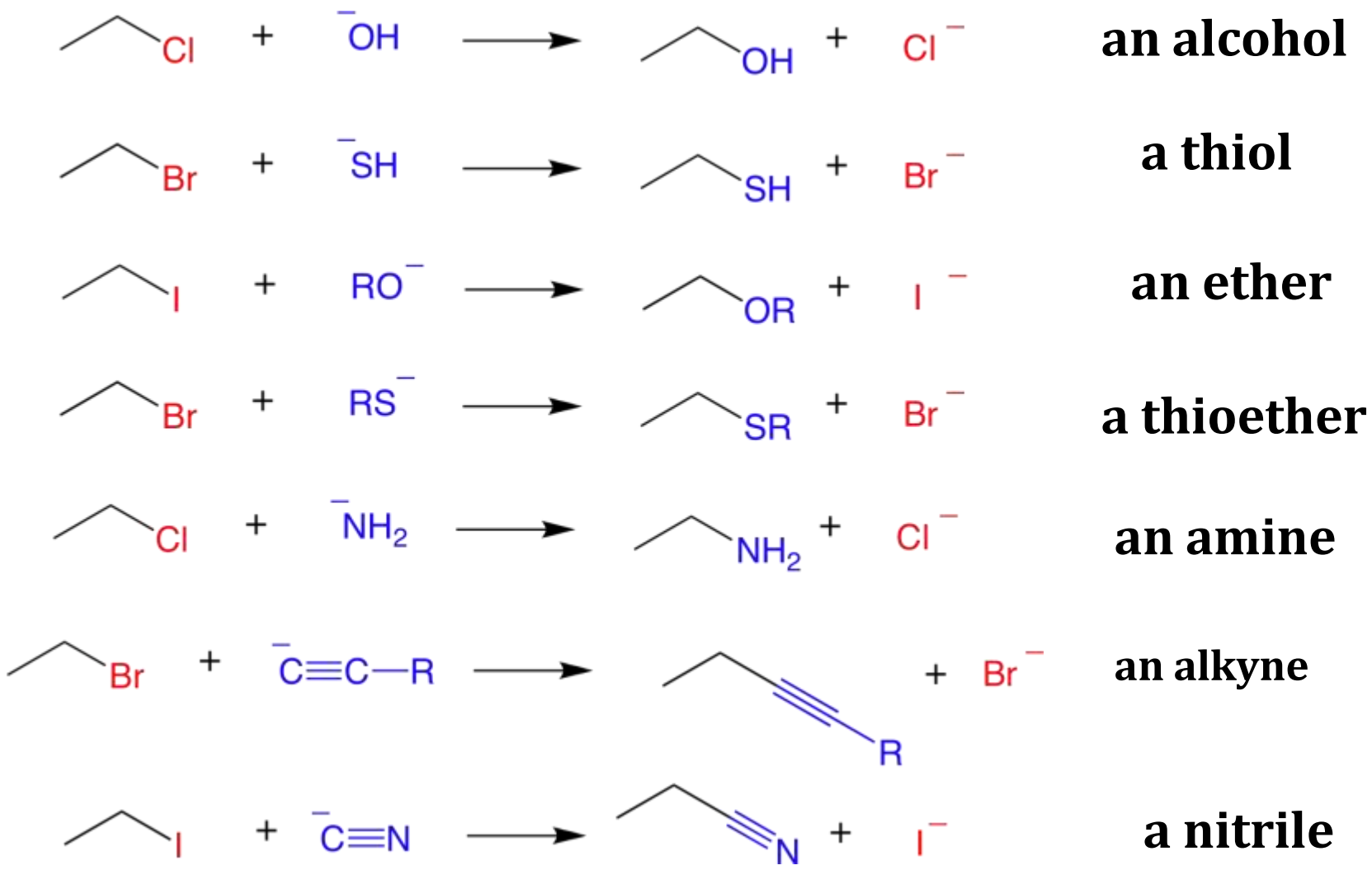
stronger base, better nucleophile	weaker base, poorer nucleophile
HO^-	H_2O
CH_3O^-	CH_3OH
H_2N^-	NH_3
$CH_3CH_2NH^-$	$CH_3CH_2NH_2$

Relative acid strengths $NH_3 < H_2O < HF$

Relative base strengths and nucleophilicities

$^-NH_2 > HO^- > F^-$

S_N2 Reactions With Alkyl Halides


Cl + OH → OH + Cl
an alcohol
Br + SH → SH + Br
a thiol
I + RO → OR + I
an ether
Br + RS → SR + Br
a thioether
Cl + NH2 → NH2 + Cl
an amine
Br + C≡C—R → R + Br
an alkyne
I + C≡N → N + I
a nitrile

For each of the following pairs of S_N2 reactions, indicate which reaction occurs faster:

a. $CH_3CH_2Br + H_2O$ or $CH_3CH_2Br + HO^-$

b. $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Br + HO^-$ or $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HBr + HO^-$

c. $CH_3CH_2Cl + CH_3O^-$ or $CH_3CH_2Cl + CH_3S^-$
(in ethanol)

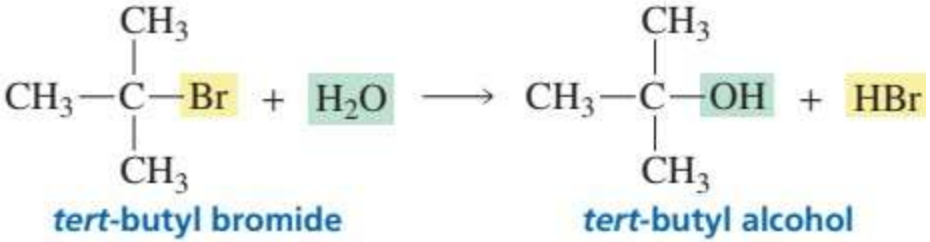
d. $CH_3CH_2Cl + I^-$ or $CH_3CH_2Br + I^-$

S_N1 Reaction

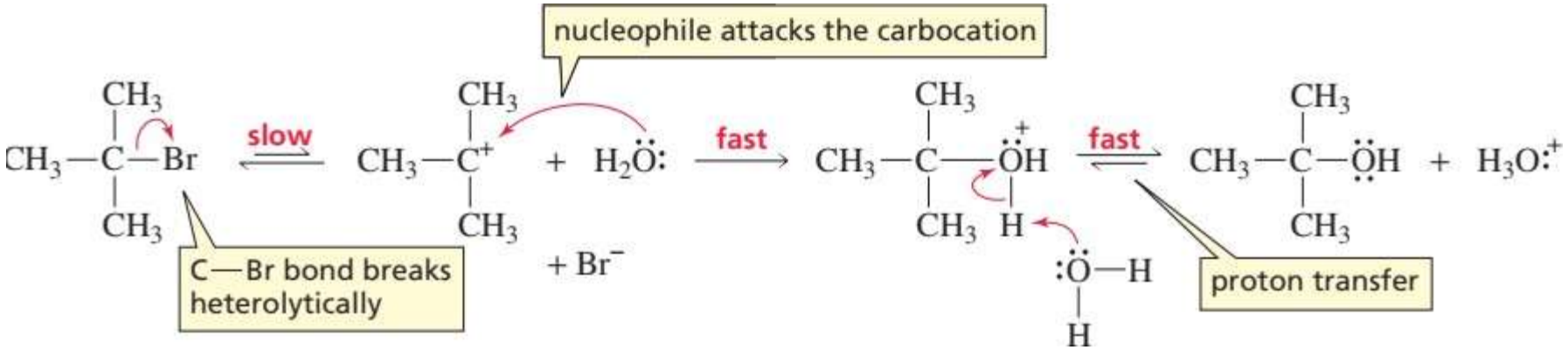
- **S_N1 reactions are nucleophilic substitution unimolecular.**
- **The rate of an S_N1 reaction depends only on the concentration of the substrate and independent of the nucleophile concentration.**
  - **Rate = k[alkyl halide]**
- **A stepwise mechanism**
  - **Because the rate of the reaction depends on the concentration of only one reactant, the reaction is a first-order reaction.**
  - **Unimolecular means that only one molecule is involved in the rate-determining step.**

S_N1 reaction of *tert*-butyl bromide

- **In S_N1 reaction the leaving group in an reaction departs *before* the nucleophile approaches.**
- **Reaction**



- **Mechanism**



Factors Affecting rate of S_N1 Reactions

1. The nature of the substrate (the alkyl halide)
2. The ability of the leaving group to leave

- The rate is independent of the power of the nucleophile.

1. The nature of the substrate (the alkyl halide)

- 3°alkyl halide >2°alkyl halide >1°alkyl halide> Me°

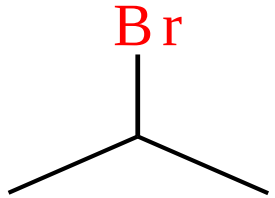
Table 10.4 Relative Rates of S_N1 Reactions for Several Alkyl Bromides (solvent is H_2O, nucleophile is H_2O)

Alkyl bromide	Class of alkyl bromide	Relative rate
$CH_3C(CH_3)_2Br$	tertiary	1,200,000
$CH_3CH(CH_3)Br$	secondary	11.6
CH_3CH_2Br	primary	1.00*
CH_3Br	methyl	1.05*

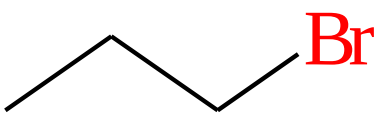
*Although the rate of the S_N1 reaction of this compound with water is 0, a small rate is observed as a result of an S_N2 reaction.

- The more substituted the carbocation is, the more stable and therefore the easier to form.

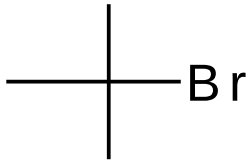
- **Arrange the following alkyl bromides in order of decreasing S_N1 reactivity in an reaction:**



A. isopropyl bromide



B. propyl bromide



C. *tert*-butyl bromide

CH_3Br

D. methyl bromide

Solution

The order of reactivity of alkyl halide in S_N1 reaction

$3^0 > 2^o > 1^o > Me^o$

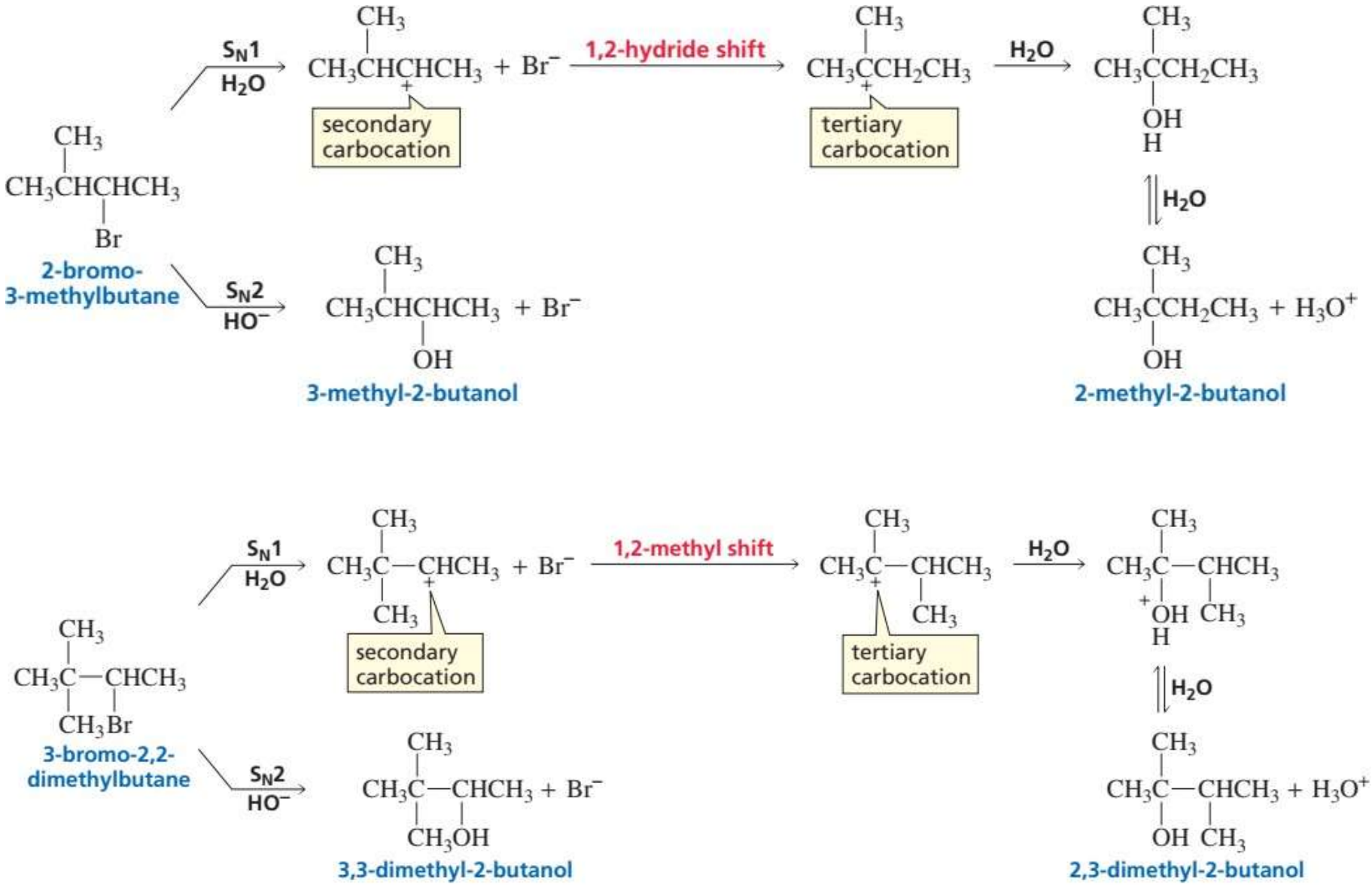
C> A> B> D

2. The nature of the leaving group

- **Relative reactivities of alkyl halides in an S_N1 reaction**

RI > RBr >RCl >RF

Carbocation Rearrangements



Comparison of S_N2 and S_N1 Reactions

S_N2

- A one-step concerted mechanism.
- A bimolecular rate-determining step.
  - Reactivity order: methyl > 1° >2° > 3° .
  - No carbocation rearrengement

S_N1

- A stepwise mechanism that forms a carbocation intermediate.
- A unimolecular rate-determining step.
- Reactivity order: 3° > 2° > 1° > methyl

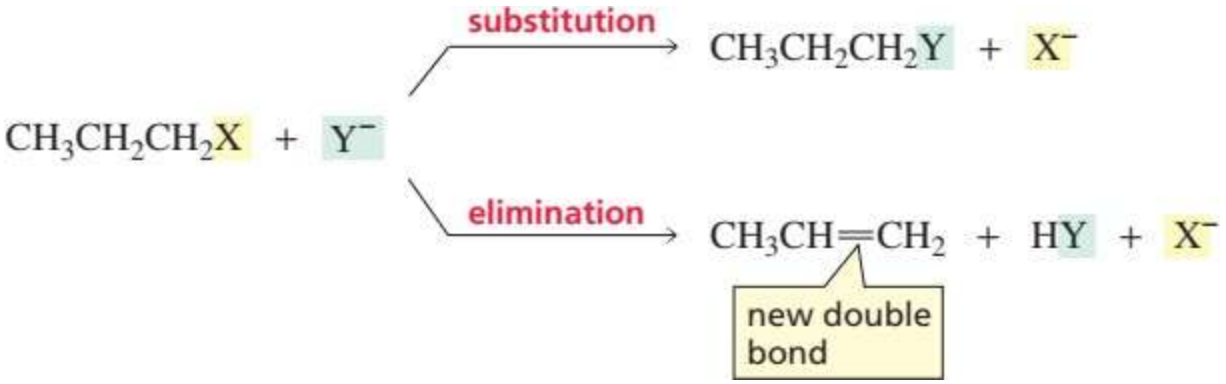
Carbocation rearrengement

Summary of the Reactivity of Alkyl Halides in Nucleophilic Substitution Reactions

Types of alkyl halides	undergo
Methyl and 1° alkyl halides	S_N2 Only
2° alkyl halides	S_N2 and S_N1
3° alkyl halides	S_N1 only

Elimination Reactions

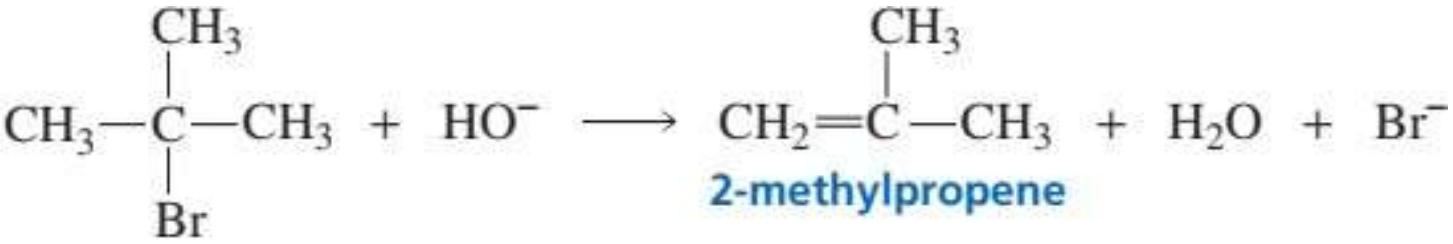
- Alkyl halide undergoes an elimination reaction
- Halogen (X) is removed from one carbon and a proton is removed from an adjacent carbon .
- The product of an elimination reaction is an alkene.



- Elimination reactions occur commonly by two mechanisms
- E2- elimination, bimolecular
- E1 – elimination unimolecular

E2 Reaction

- "E" stands for elimination and "2" stands for bimolecular.
- Rate of E2 reaction depends on both the concentration of the base and the alkyl halide.
  - Rate = k[alkyl halide][base]
- Second order
- The reaction of *tert*-butylbromide with hydroxide ion is an example of an E2 reaction;

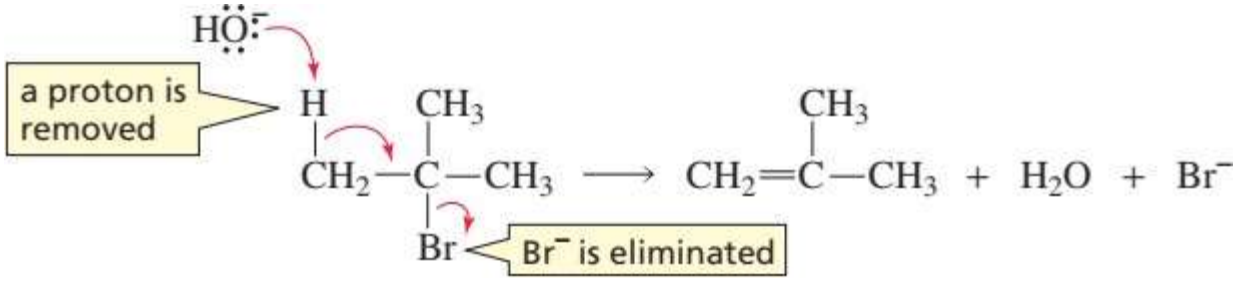


tert-butyl bromide

2-methylpropene

Mechanism of E2

- **E2 reactions are concerted (one-step) mechanism.**
  - **The two groups depart simultaneously**
  - **The proton and the bromide ion are removed in the same step, so no intermediate is formed.**
- **Mechanism of E2 reaction**



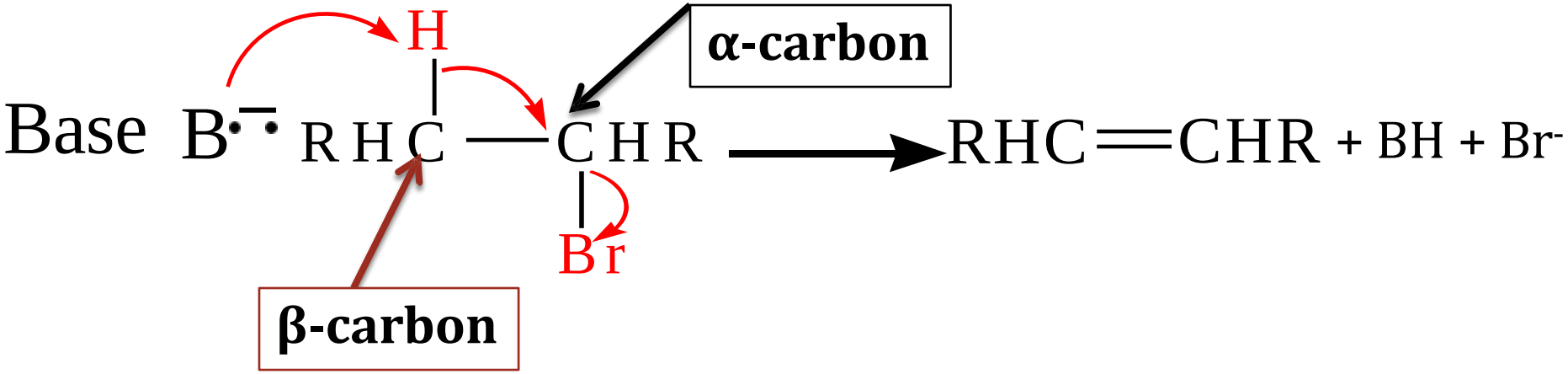
❖ **In the E2 mechanism the three key elements**

C-H bond breaking
C=C bond formation
C-X bond breaking

All are taking place at the same transition state.

- **Removal of a proton and a halide ion is called dehydrohalogenation.**

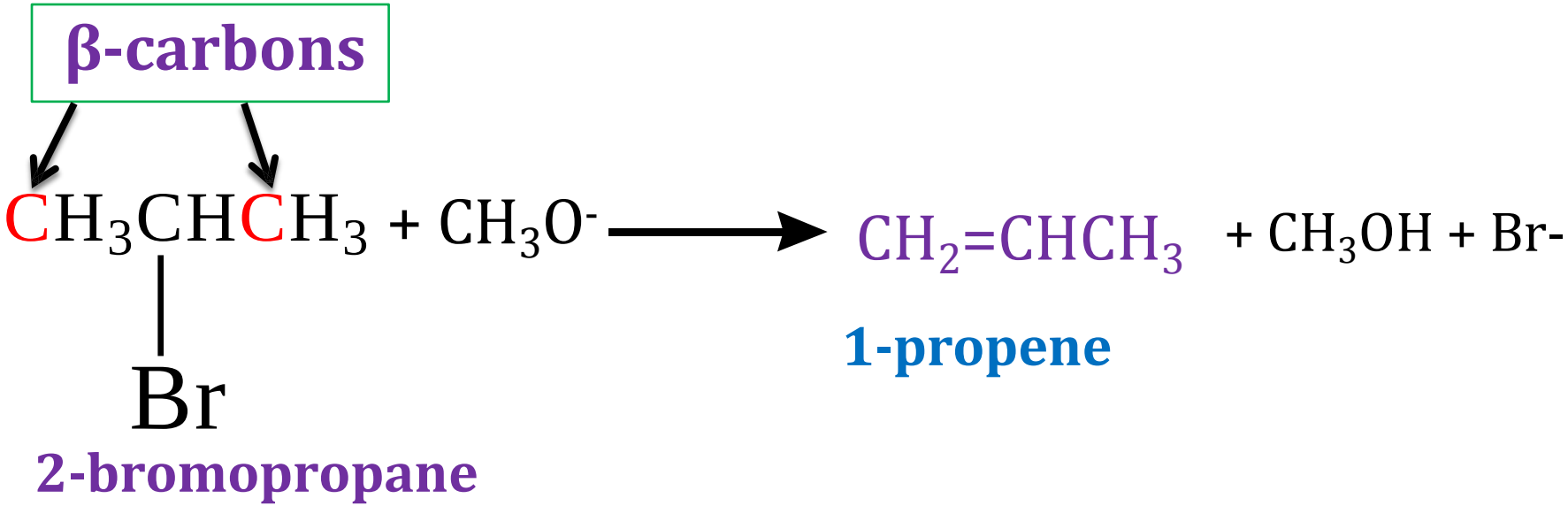
- **The carbon to which the halogen is attached is called the α-carbon.**
- **A carbon adjacent to the α -carbon is called a β-carbon.**
- **Elimination reaction is initiated by removing a proton from a β -carbon, an E2 reaction is sometimes called a β – elimination reaction(1,2-elimination reaction).**



- **E2 reactions occur when a 2° or 3° alkyl halide is treated with a strong base such as OH^-, OR^-, NH_2^-, H^-, etc**

Regioselectivity of the E2 Reaction

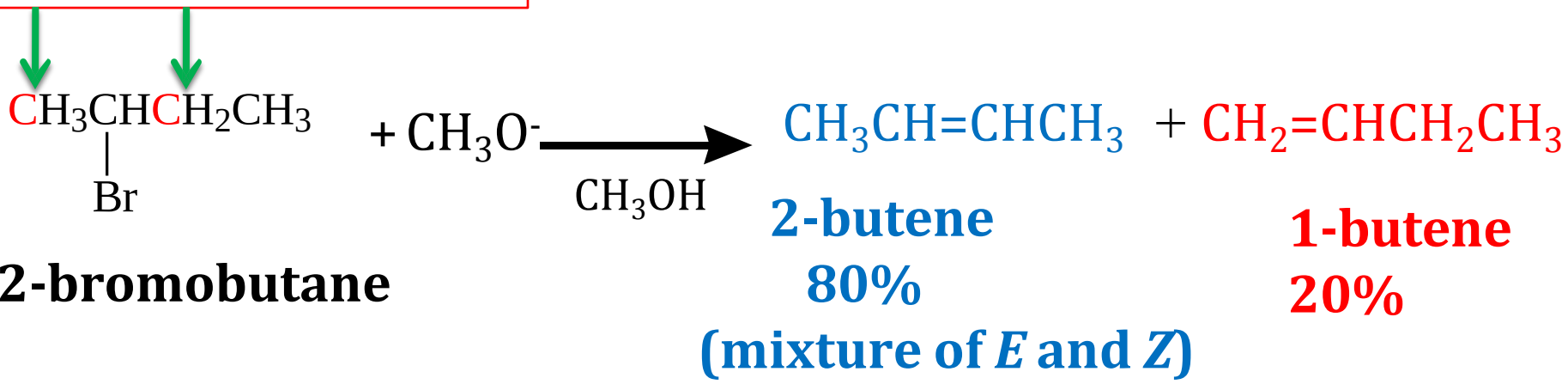
- **If the two β-carbons are identical gives the same product.**
- **Example 2-bromopropane**



Different β -carbons

- If the two different β –carbons present in the reactant , two elimination products are formed.
- Example, 2-bromobutane reacts with a base

different β –carbons



2-bromobutane

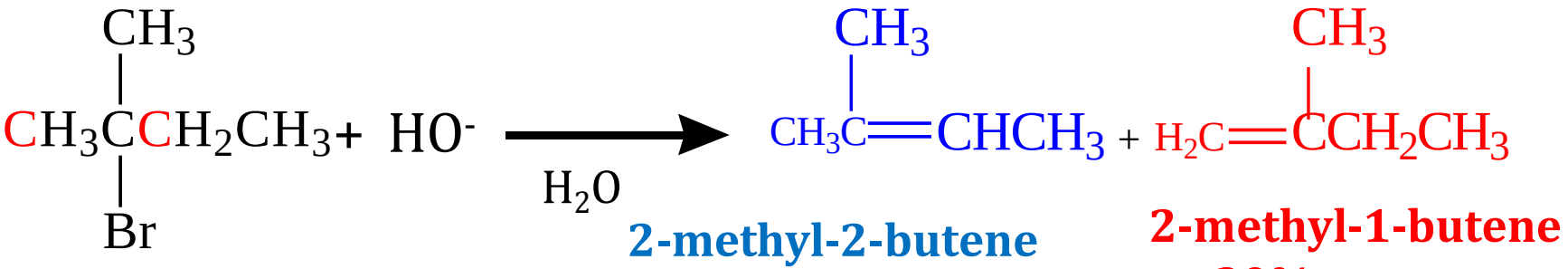
2-butene
80%
(mixture of *E* and *Z*)

1-butene
20%

The stability of an alkene depends on the number of alkyl substituents bonded to its sp^2 carbons:

- The greater the number of substituents, the more stable is the alkene

- **The major product of an E2 reaction is the most stable alkene.**
- **Example the reaction 2-bromo-2-methylbutane with hydroxide ion.**



2-bromo-2-methylbutane

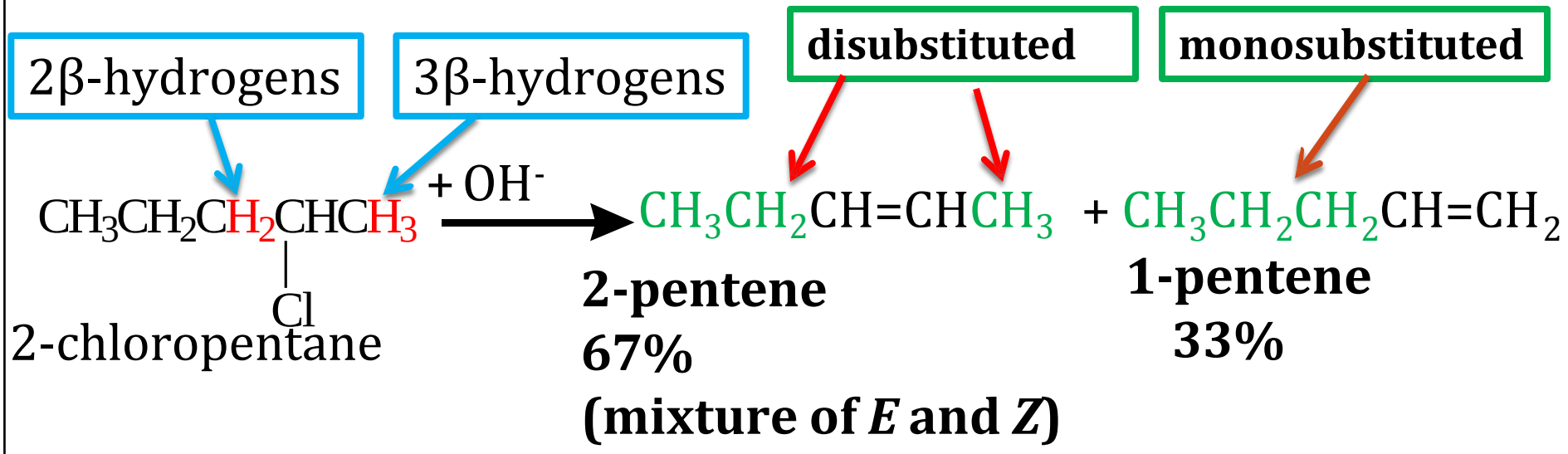
2-methyl-2-butene
70%
Major product

2-methyl-1-butene
30%

- **Because 2-methyl-2-butene is the more substituted alkene (it has a greater number of alkyl substituents bonded to its sp^2 carbons).**
- **it is the more stable of the two alkenes and therefore, is the major product of the elimination reaction.**

Saytzeff's (Zaitsev)rule

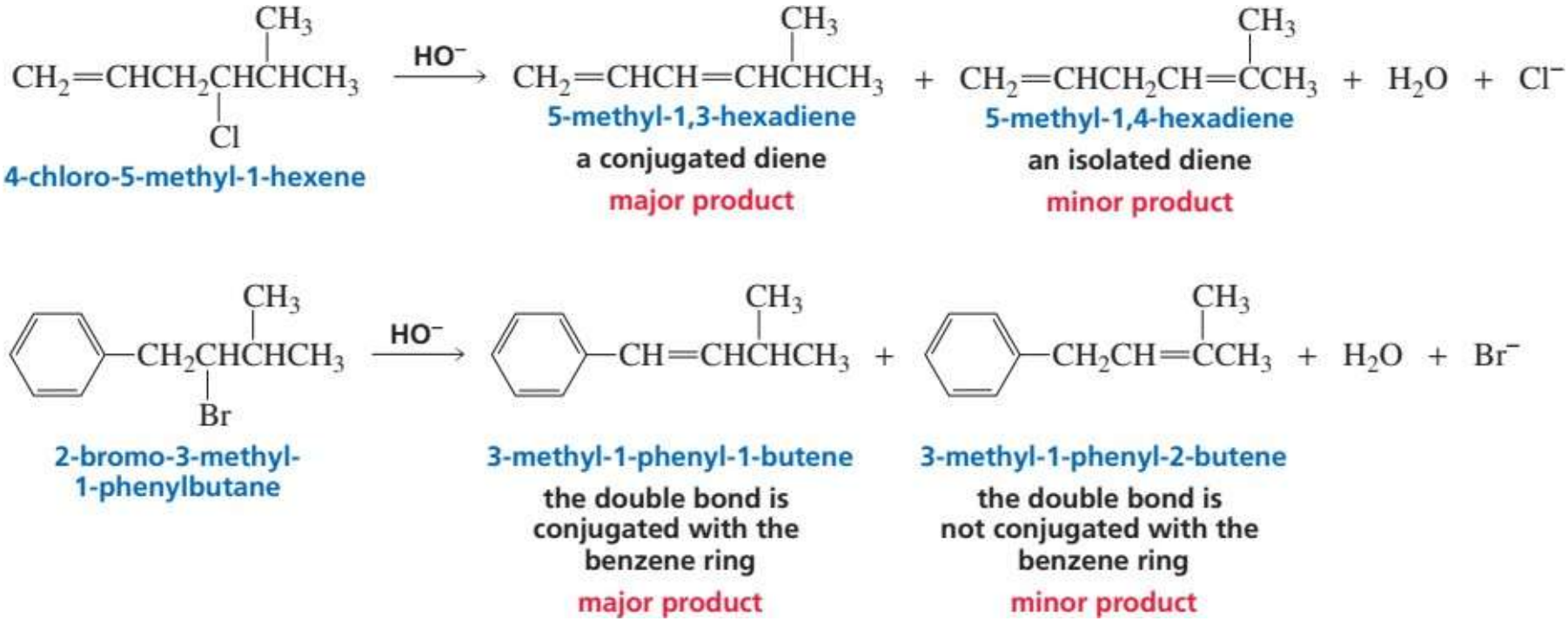
- **In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates(Major product).**
- **He pointed out *that the more substituted alkene product is obtained when a proton is removed from the β-carbon that is bonded to the fewest hydrogens*.**
- Example 2-chloropentane



- **Relative reactivities of alkyl halides in an E2 reaction is,**
  - **tertiary alkyl halide > secondary alkyl halide > primary alkyl halide**

Exception of Saytzeff's rule

- **The more substituted alkene is not always the more stable alkene.**
- **The conjugated alkene is the more stable alkene even though it is not the most substituted alkene.**

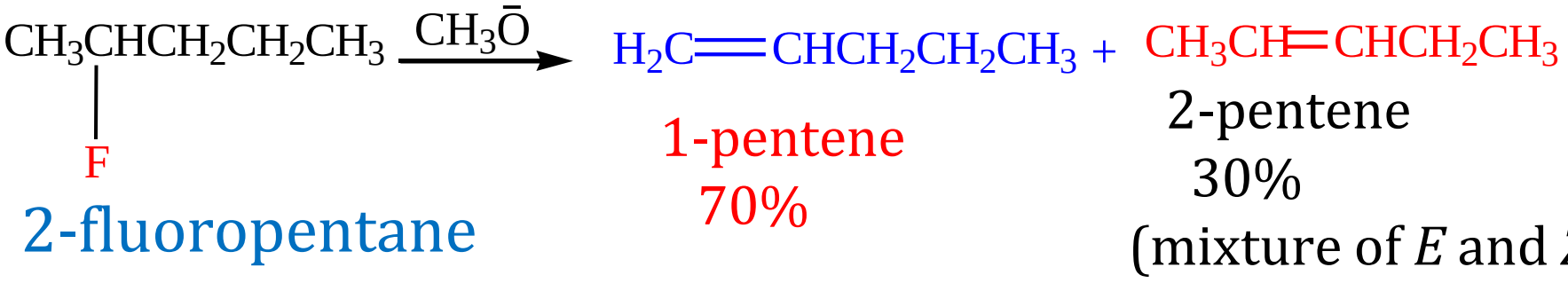


Nature of leaving groups

- **The major product of an E2 dehydrohalogenation of**
- **alkyl chlorides**
- **alkyl bromides**
- **alkyl iodides**

more substituted alkene as major product

- **alkyl fluorides - the less substituted alkene as major product.**



2-fluoropentane

1-pentene
70%

2-pentene
30%
(mixture of *E* and *Z*)

When a hydrogen and a chlorine, bromine, or iodine are eliminated from an alkyl halide, the halogen starts to leave as soon as the base begins to remove the proton.

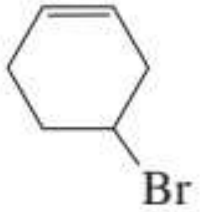
Give the major elimination product obtained from an E2 reaction of each of the following alkyl halides with hydroxide ion:

a. $CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3$

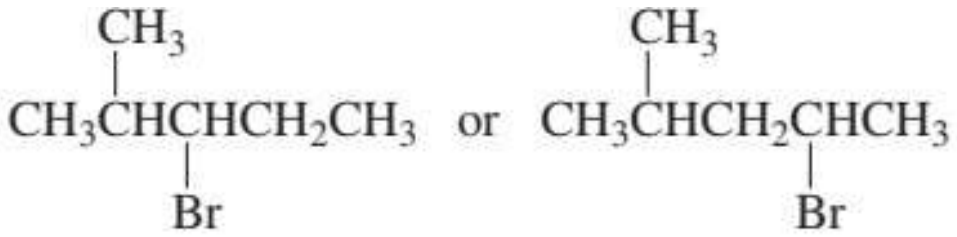
b. $CH_3\underset{\displaystyle F}{\underset{|}{C}}HCH_2CH_3$

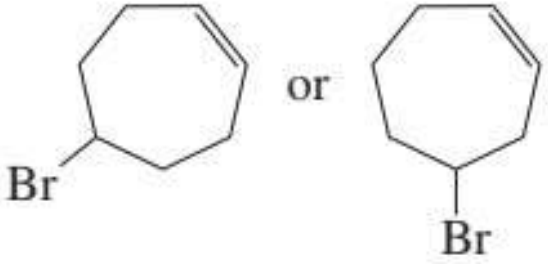
c. $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3$

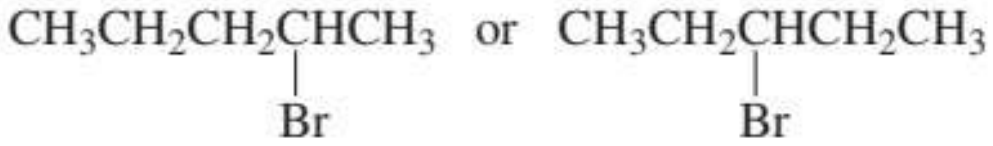
d. $CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH{=}CH_2$

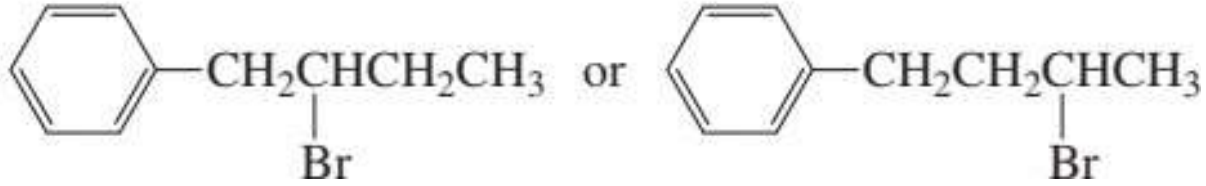
e. 

f. $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH\underset{\displaystyle F}{\underset{|}{C}}HCH_2CH_3$

a. 
CH3
CH3CHCHCH2CH3
Br
or
CH3
CH3CHCH2CHCH3
Br

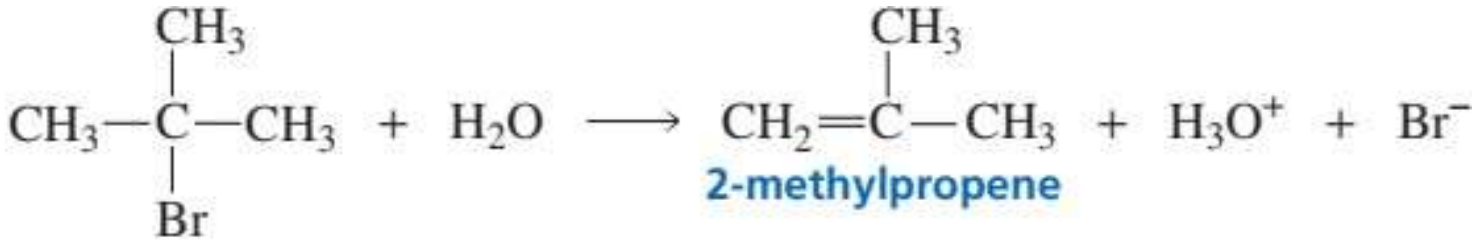
b. 
Br
or
Br

c. 
CH3CH2CH2CHCH3
Br
or
CH3CH2CHCH2CH3
Br

d. 
CH2CHCH2CH3
Br
or
CH2CH2CHCH3
Br

E1 Reaction

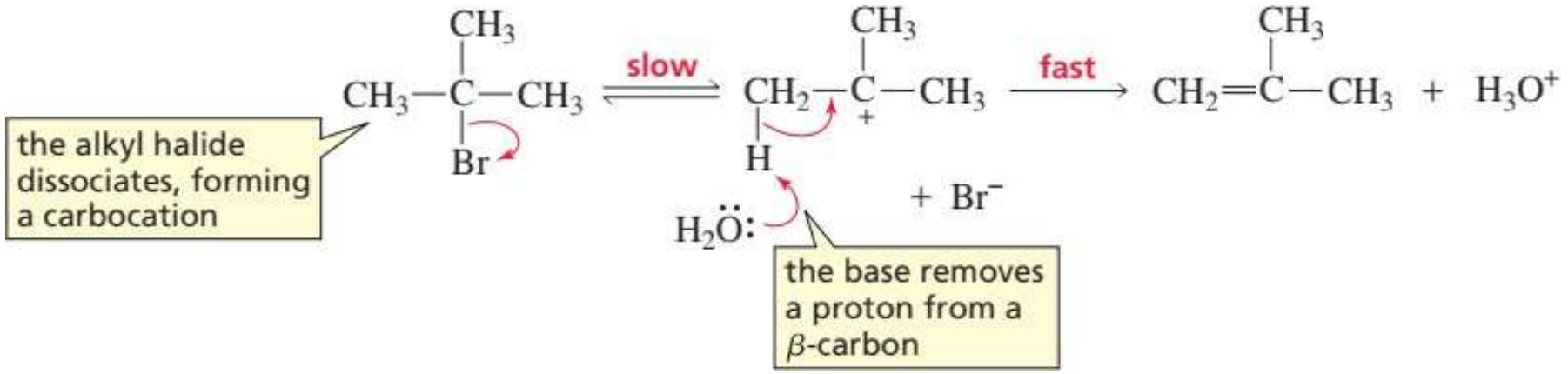
- ***Elimination, unimolecular***
- **An E1 reaction is a first-order elimination reaction because the rate of the reaction depends only on the concentration of the alkyl halide.**
  - **Rate = k[alkyl halide]**
  - **Only the alkyl halide is involved in the rate-determining step of the reaction. Therefore, there must be at least two steps in the reaction.**



tert-butyl bromide

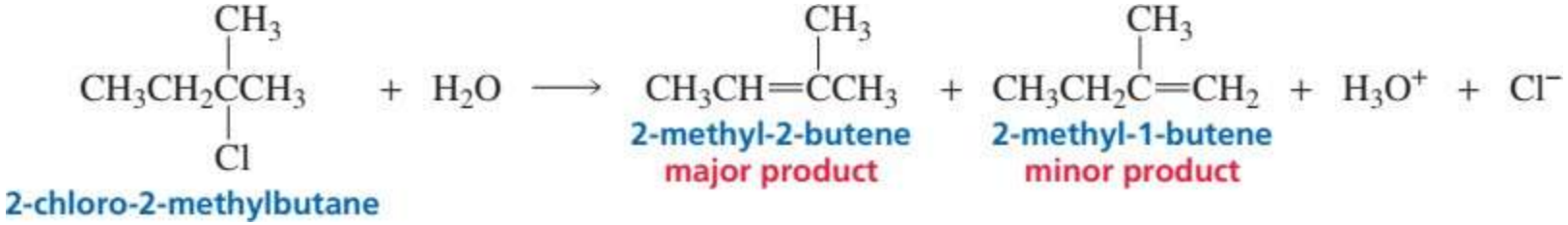
2-methylpropene

Reaction mechanism of E1



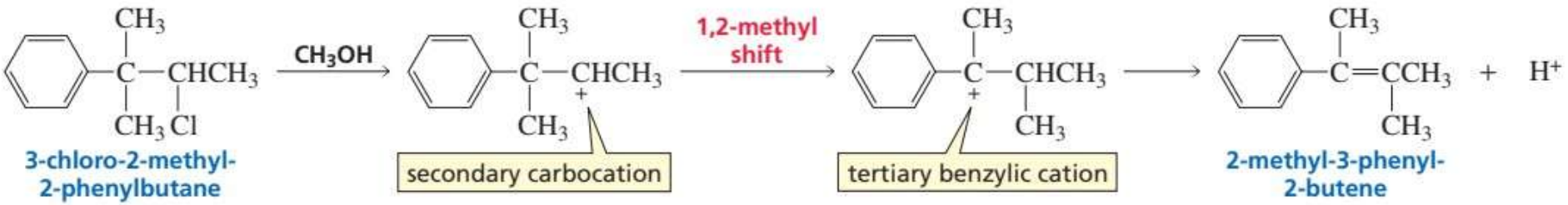
E1 reaction also follow Zaitsev's rule.

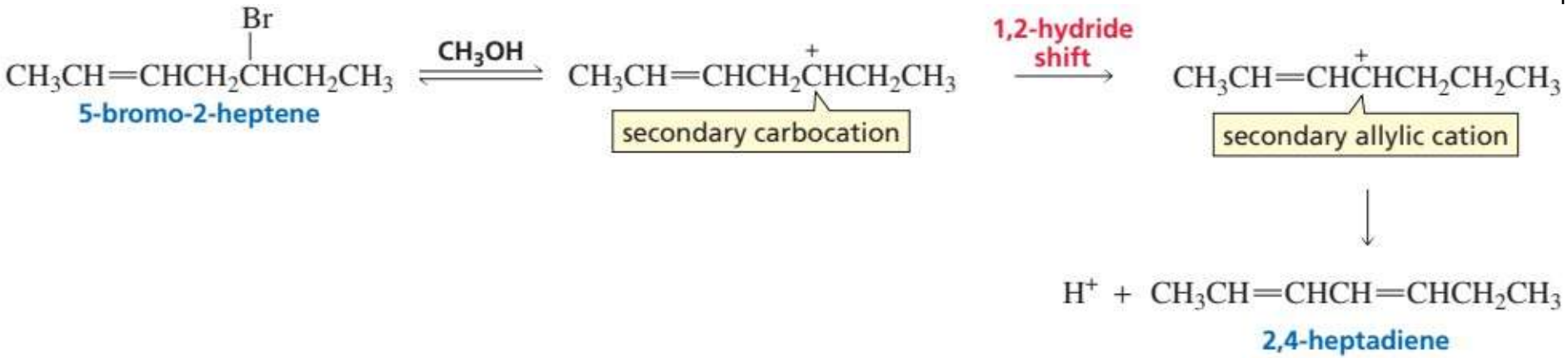
Example the reaction of 2-chloro-2-methylbutane with water



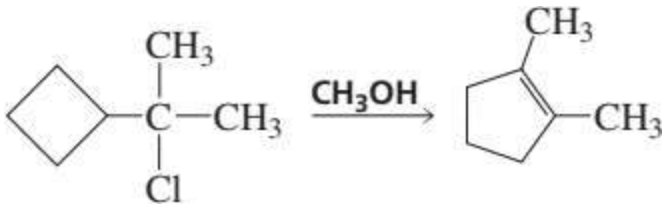
- **Relative reactivities of alkyl halides in an E1 reaction = relative stabilities of carbocations.**
  - **3° > 2° > 1°**
- **Relative reactivities of alkyl halides in an E1 reaction**
  - **RI >RBr > RCl > RF**

Carbocation rearrangement

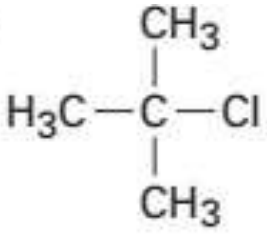
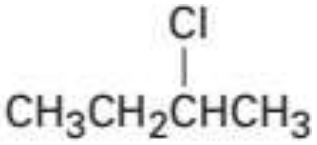


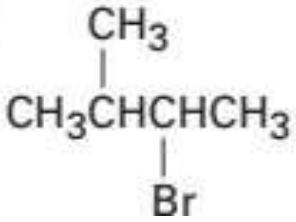
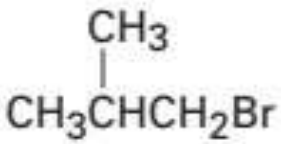


- **Propose a mechanism for the following reaction:**

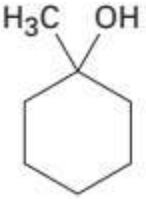


- **Order each set of compounds with respect to SN2 reactivity.**

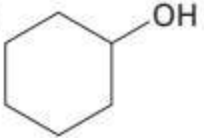
(a)  $CH_3CH_2CH_2Cl$ 

(b)   CH_3Br

- **Predict the product(s) of the following reactions:**

(a)  $\xrightarrow[\text{Ether}]{\text{HBr}}$?

(b) $CH_3CH_2CH_2CH_2OH \xrightarrow{SOCl_2}$?

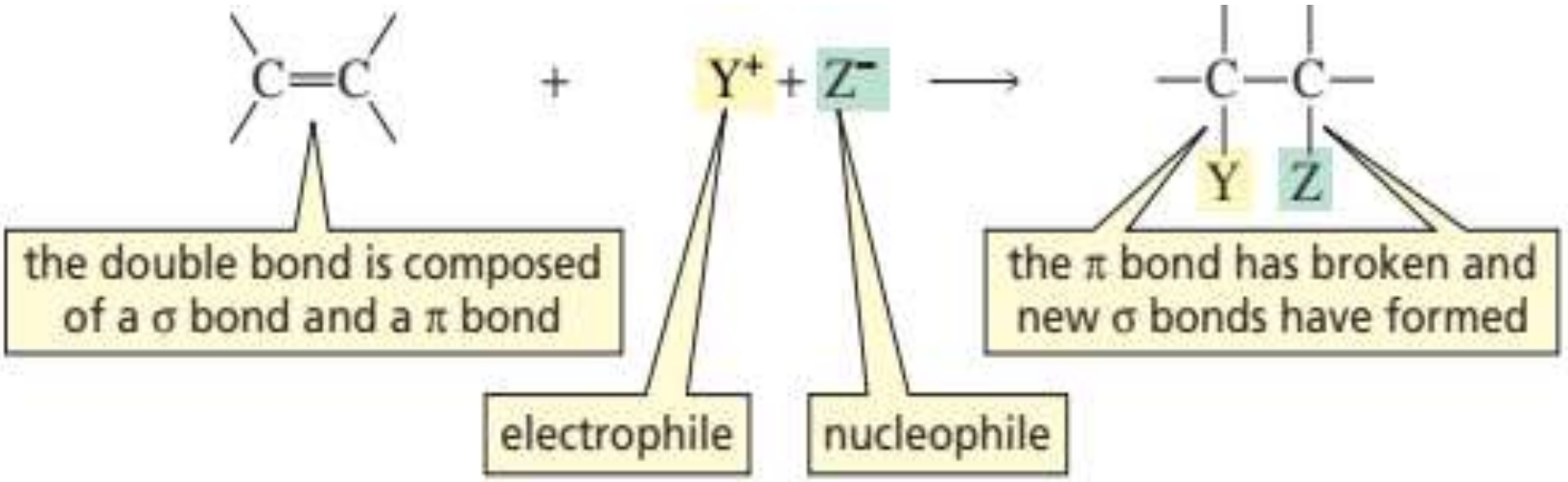
(c)  $\xrightarrow[\text{Ether}]{PBr_3}$?

(d) $CH_3CH_2CH(Br)CH_3 \xrightarrow[\text{Ether}]{\text{Mg}}$ **A** $\xrightarrow{H_2O}$ **B**

Addition reaction

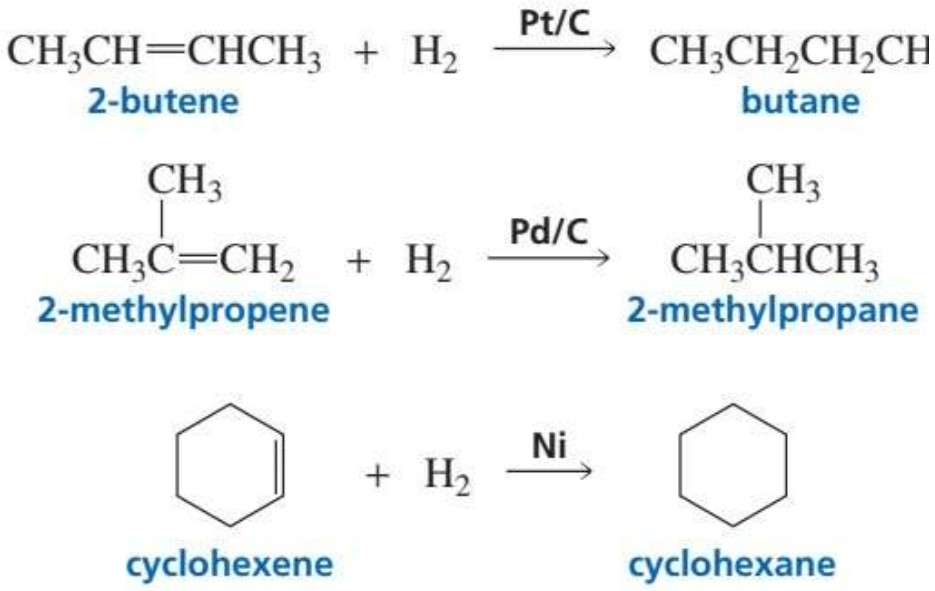
- **Addition reaction** Occur when two reactants add together to form a single new product with no atoms left over."
- $CH_2=CH_2 + HCl \longrightarrow CH_3CH_2Cl$

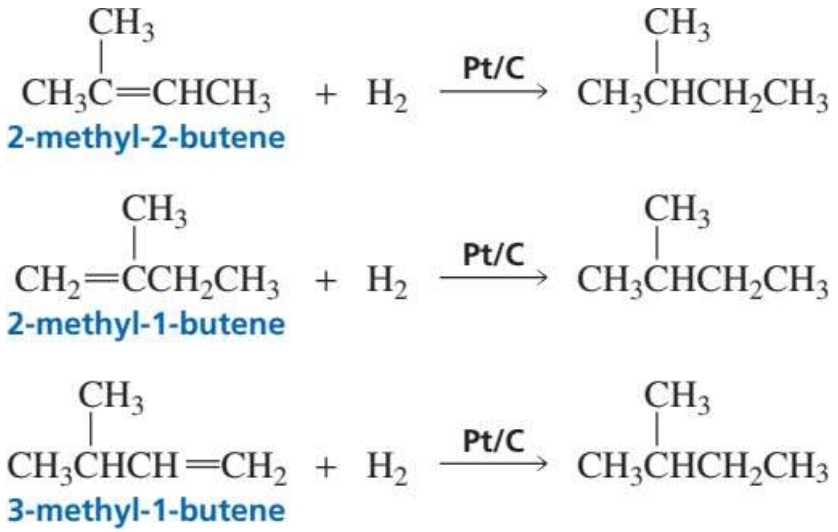
- Alkenes are nucleophiles and react with electrophiles in **electrophilic addition reactions**



A. Addition of Hydrogen

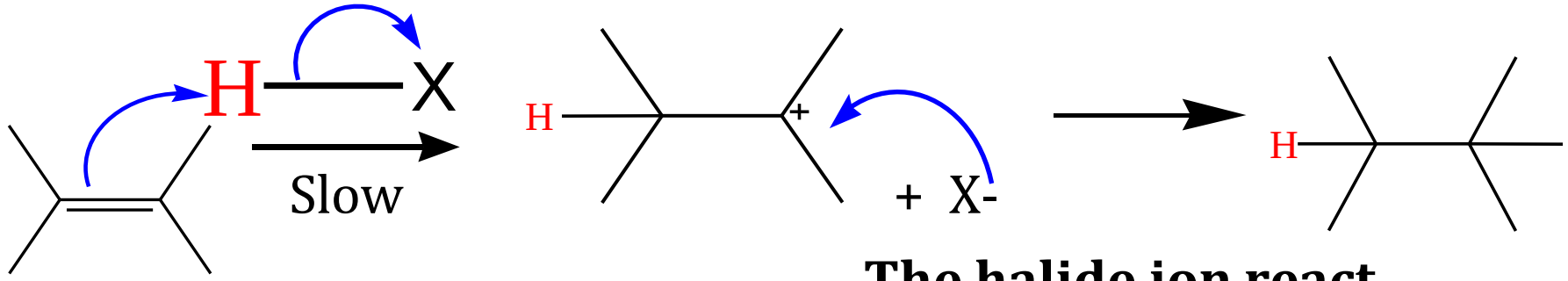
- **Hydrogen(H_2) adds to the double bond of an alkene to form an alkane**
  - **A catalyst such as platinum or palladium is used (Transition metals).**
  -





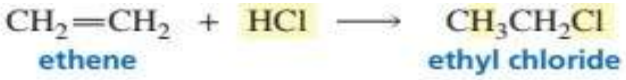
B. Hydrohalogenation:

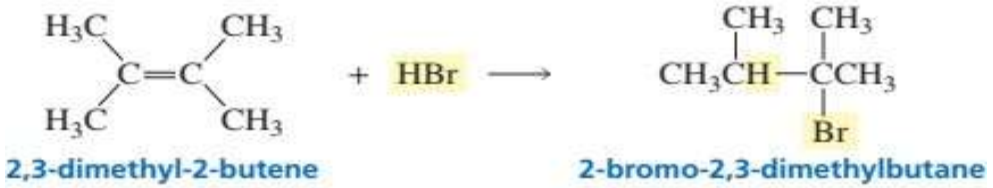
- **Addition of Hydrogen Halides(HCl, HBr, or HI)**
- **product alkyl halide:**

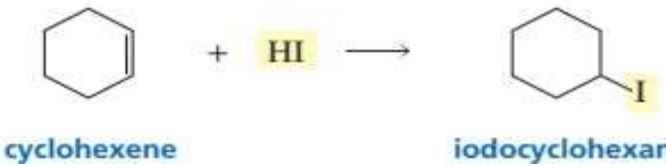


The π bond of the alkene form a bond with a proton from HX

The halide ion react with carbocation

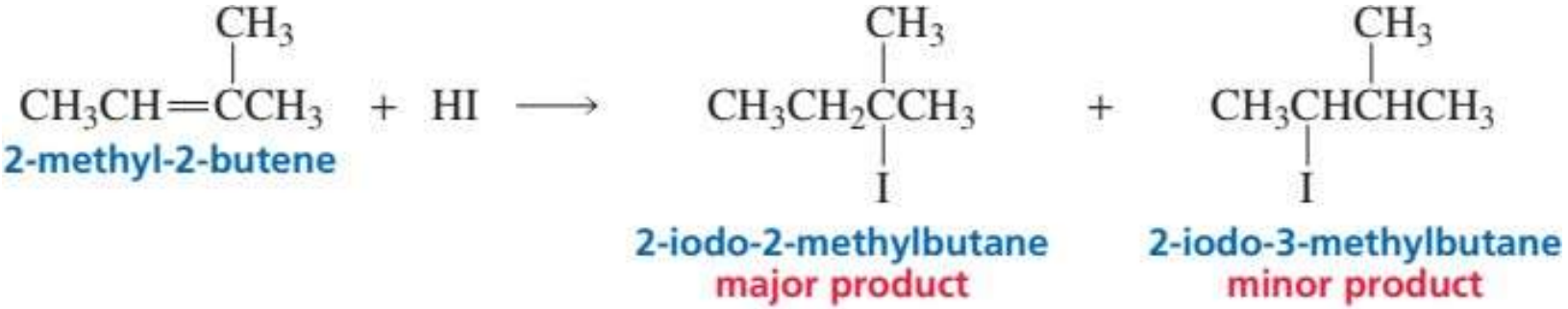


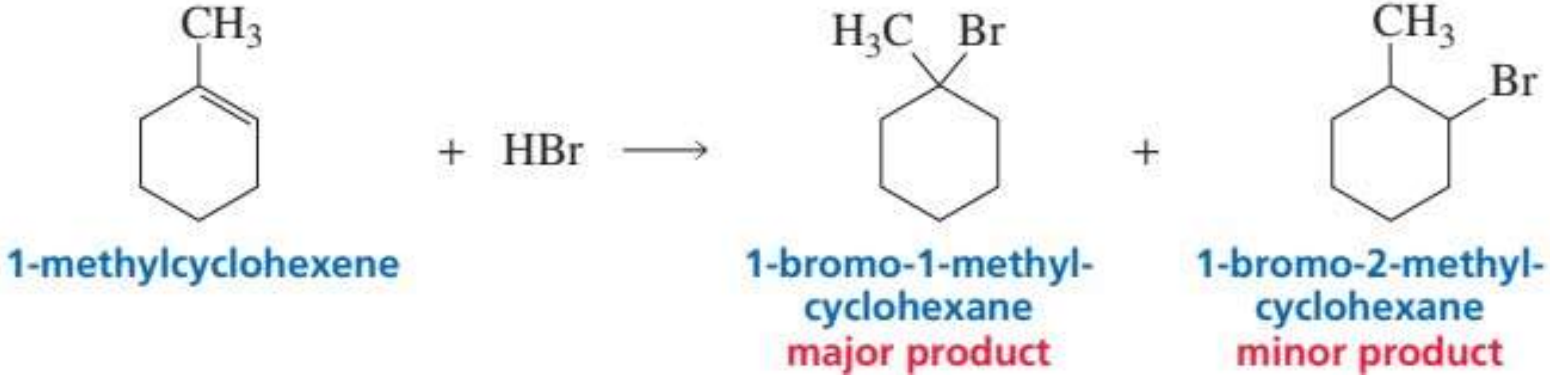




Regioselectivity HX

-Markovnikov's rule: H added to double bonded carbon that has the greater number of H and halogen added to the other carbon.





1-Butene Hydrogen bromide 2-Bromobutane (80%)

2-Methylpropene Hydrogen bromide 2-Bromo-2-methylpropane (90%)

1-Methylcyclopentene Hydrogen chloride 1-Chloro-1-methylcyclopentane (100%)

Mechanistic basis for Markovnikov's rule

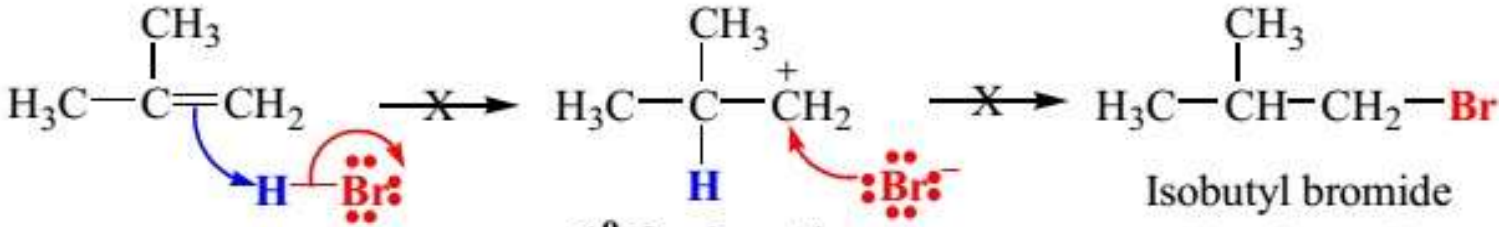
Addition of HBr to 2-Methylpropene

This reaction takes place:

3° Carbocation
(more stable carbocation)

tert-Butyl bromide
Actual product

This reaction ***does not*** occur appreciably:

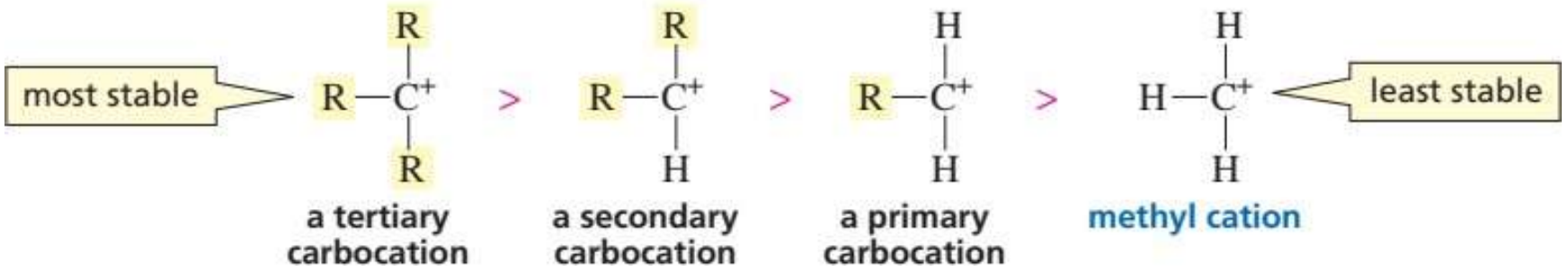


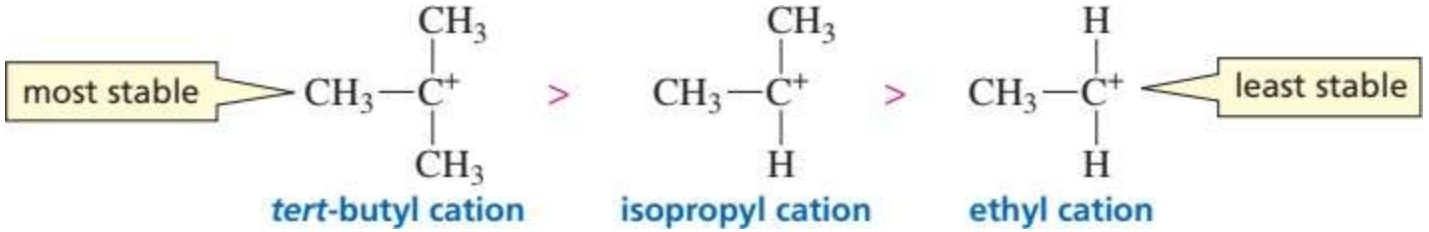
1° Carbocation
(less stable carbocation)

Isobutyl bromide
Not formed

Carbocation Stability

relative stabilities of carbocations





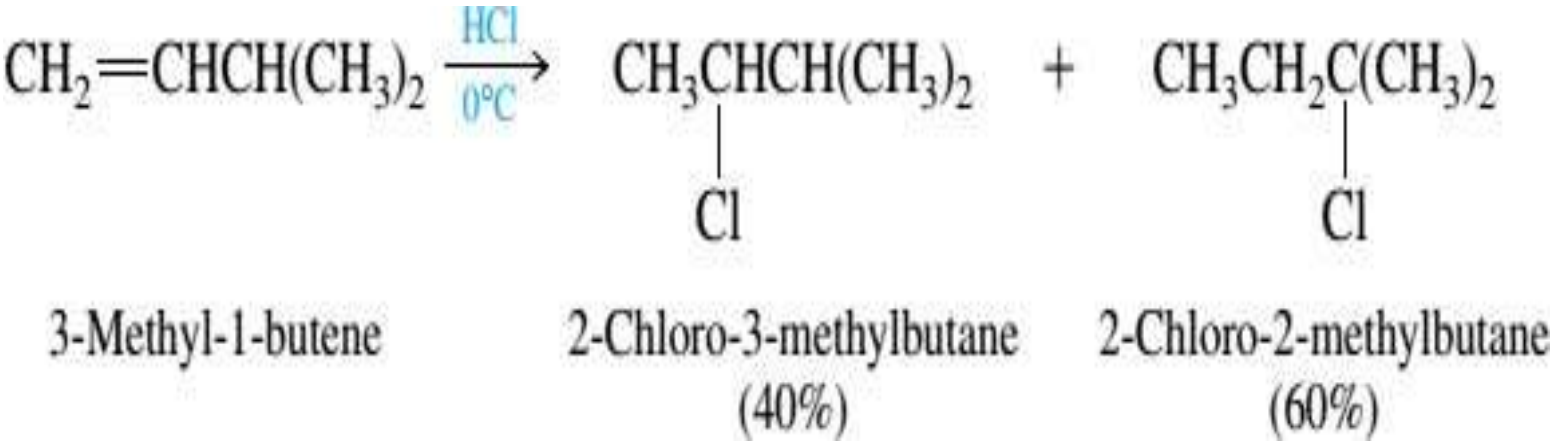
List the carbocations in order of decreasing stability.

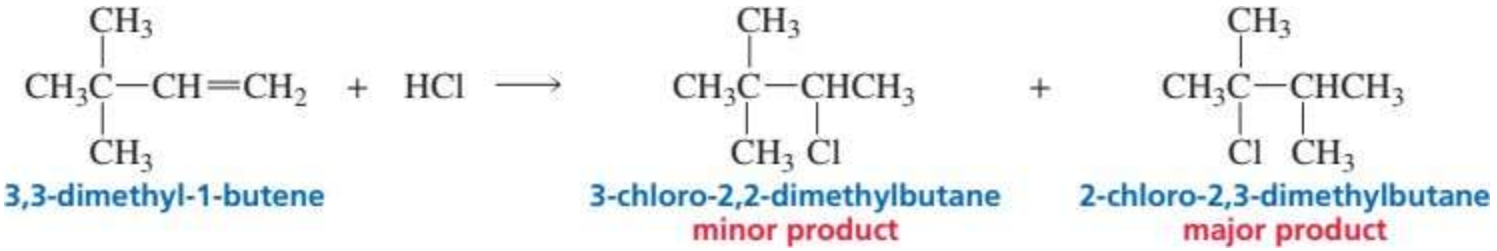
a. $CH_3CH_2\overset{+}{C}(CH_3)_2$ $\quad$ $CH_3CH_2\overset{+}{C}HCH_3$ $\quad$ $CH_3CH_2CH_2\overset{+}{C}H_2$

b. $CH_3CH(Cl)CH_2\overset{+}{C}H_2$ $\quad$ $CH_3CH(CH_3)\overset{+}{C}HCH_2CH_3$ $\quad$ $CH_3CH(F)CH_2\overset{+}{C}H_2$

Carbocation Rearrangements

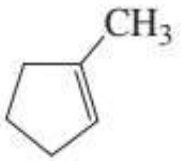
- **Carbocation rearrangement occur(secondary to tertiary) via 1,2 hydride shift or 1,2 methyl shift to form more stable Carbocation.**

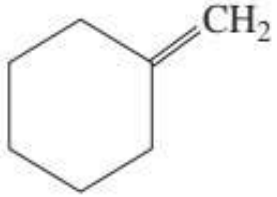




What would be the major product obtained from the addition of HBr to each of the following compounds?

a. $CH_3CH_2CH{=}CH_2$

c. 

e. 

b. $CH_3CH{=}C(CH_3)CH_3$

d. $CH_2{=}C(CH_3)CH_2CH_2CH_3$

f. $CH_3CH{=}CHCH_3$

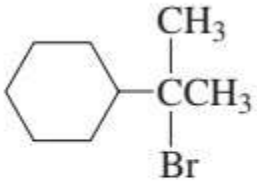
What alkene should be used to synthesize 3-bromohexane?

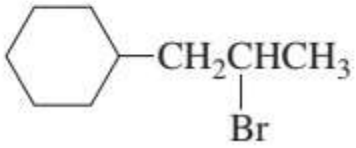
$$? + HBr \longrightarrow CH_3CH_2CH(Br)CH_2CH_2CH_3$$

3-bromohexane

What alkene should be used to synthesize each of the following alkyl bromides?

a. $CH_3C(CH_3)(Br)CH_3$

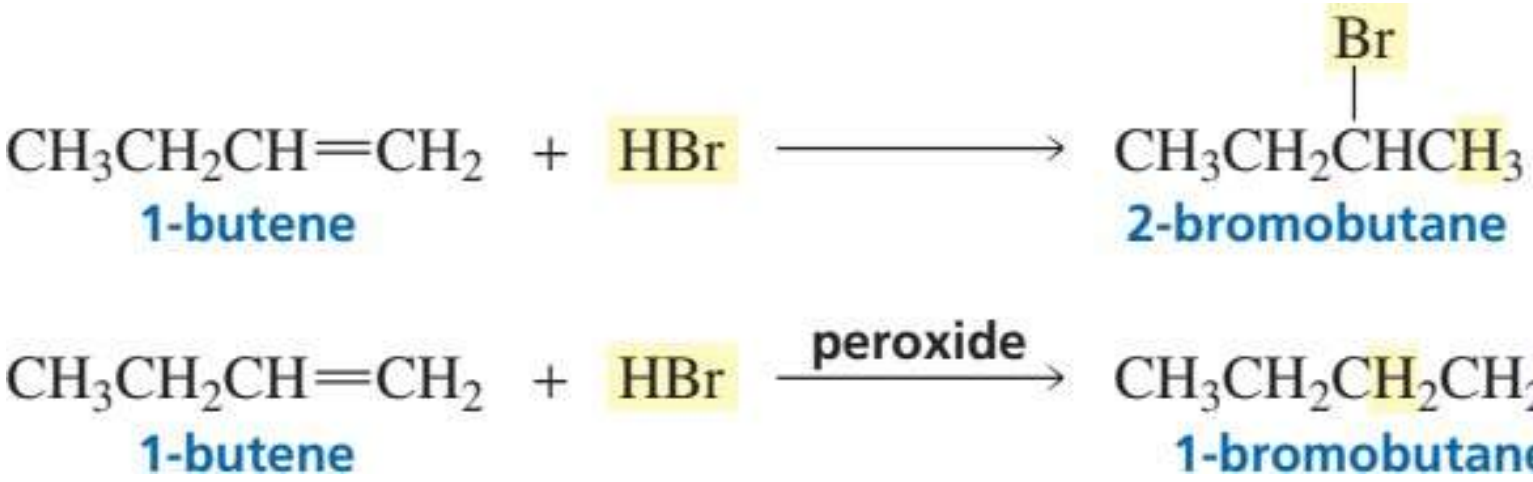
c. 

b. 

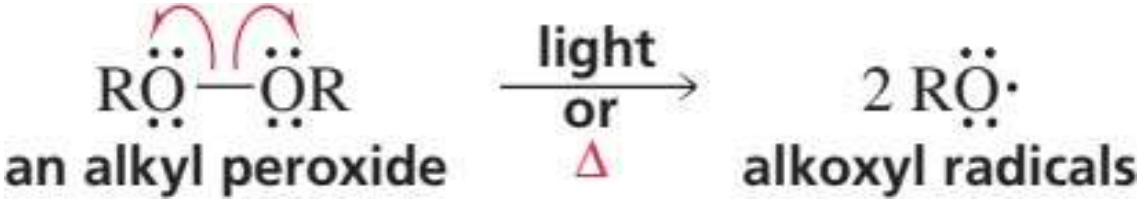
d.

Anti-Markovnikov's Addition

- **Hydrogen added to sp^2 carbon which bonded to fewer hydrogen and halogen added to sp^2 carbon which bonded a greater hydrogen in the presence of peroxides(ROOR).**

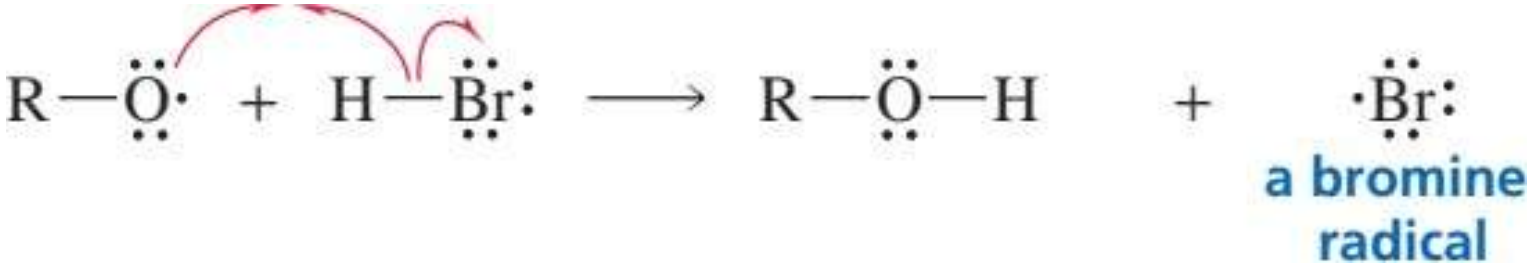


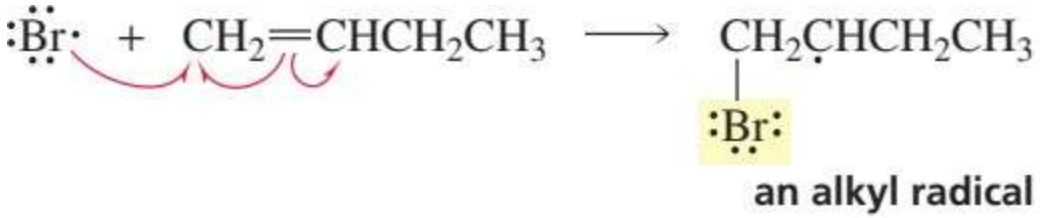
Mechanism basis Anti-Markovnikov's

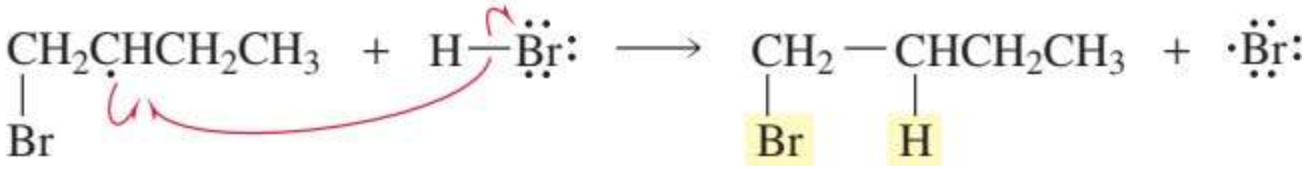


A radical is highly reactive

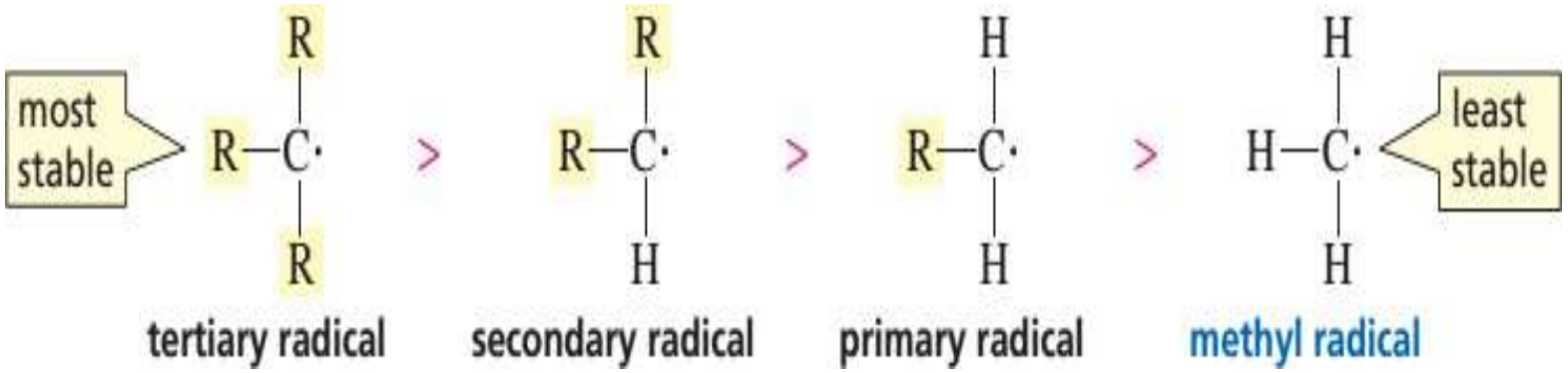
2nd hydrogen abstract from HBr by alkoxy radical





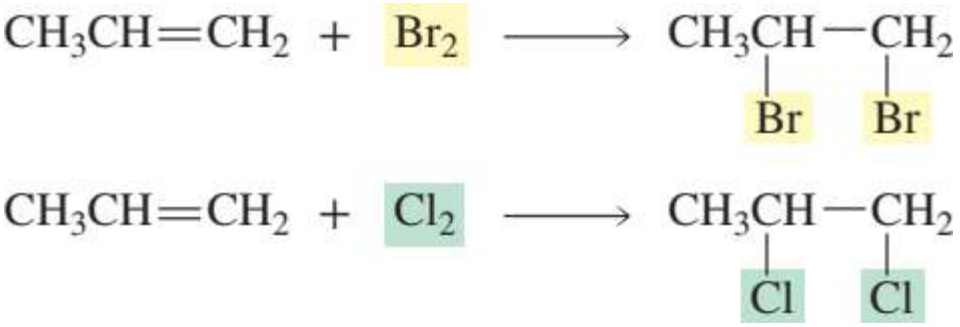


Relative stability of radicals

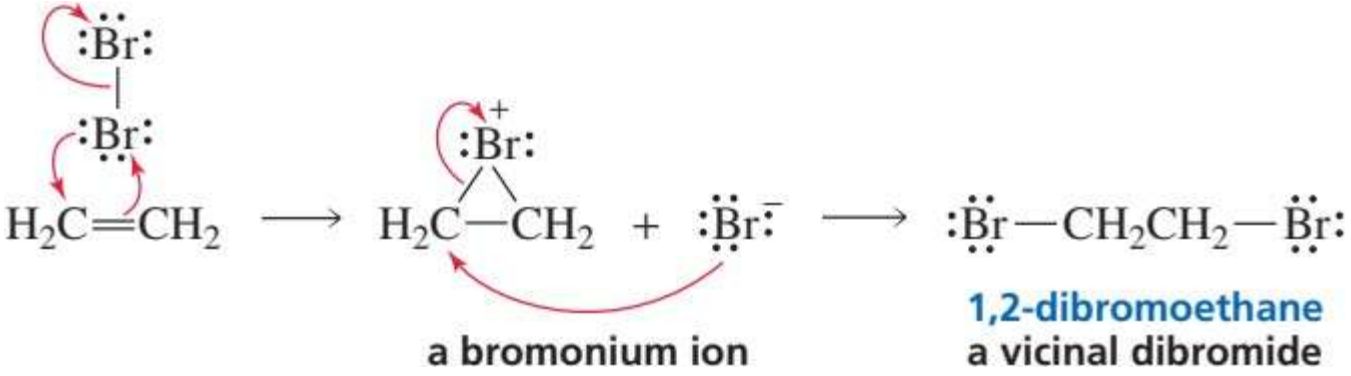


C. Halogenation

- **Addition of Halogens**
- **A halogen atom adds to each carbon atom of a double bond.**
  - **product 1,2-dihaloalkanes (vicinal dihaloalkanes),**

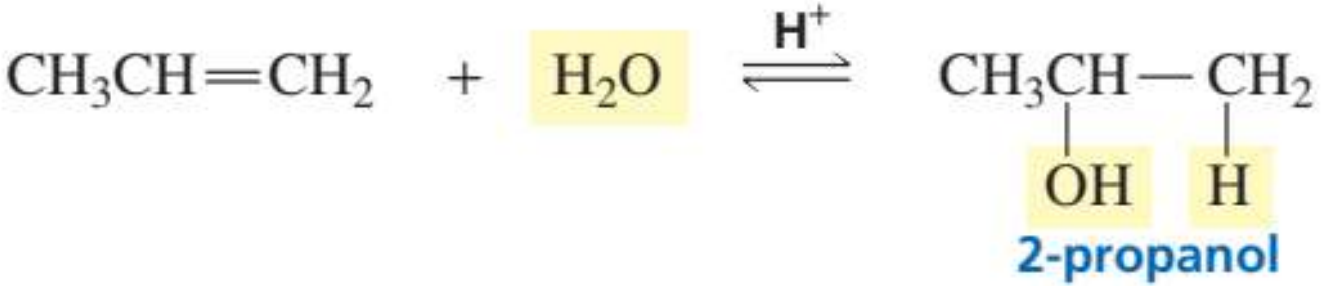


Mechanism

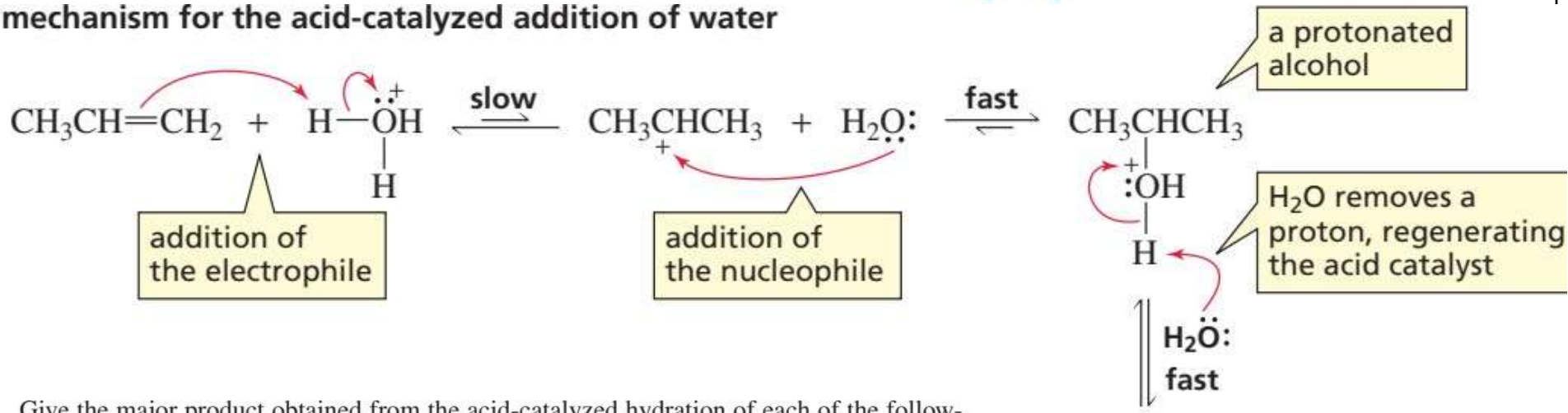


D. Hydration (addition of water):

- **Water added to C=C to give an alcohol.**
- **Acid catalyst (concentrated sulfuric acid).**
- **A regioselective reaction (Markovnikov's rule).**



mechanism for the acid-catalyzed addition of water

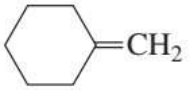


Give the major product obtained from the acid-catalyzed hydration of each of the following alkenes:

a. $CH_3CH_2CH_2CH{=}CH_2$

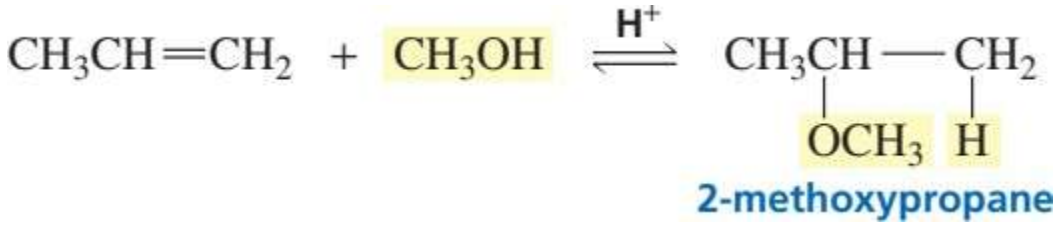
b.

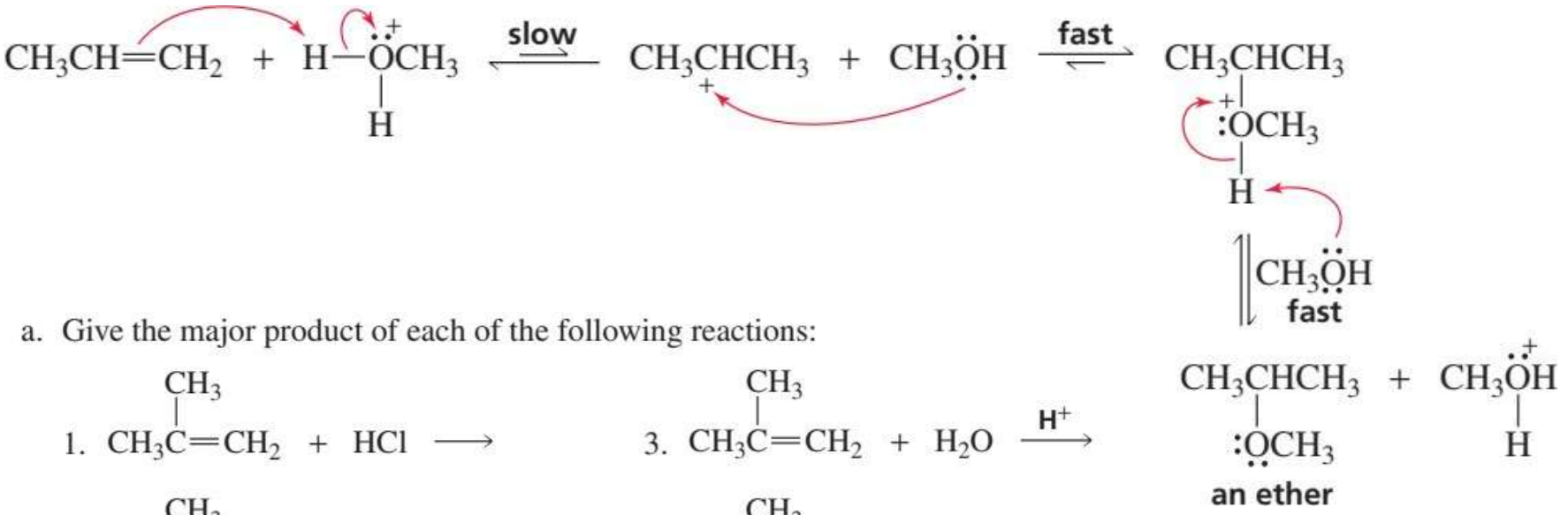
c. $CH_3CH_2CH_2CH{=}CHCH_3$

d. 

Addition of Alcohols

- product of the reaction is an ether.
- acid catalyst



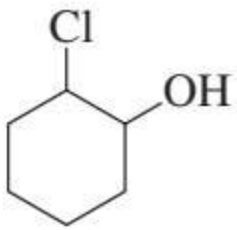


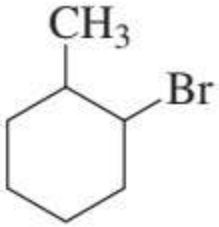
a. Give the major product of each of the following reactions:

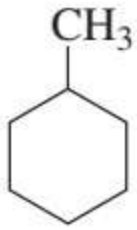
1. $CH_3C(CH_3){=}CH_2 + HCl \longrightarrow$
2. $CH_3C(CH_3){=}CH_2 + HBr \longrightarrow$
3. $CH_3C(CH_3){=}CH_2 + H_2O \xrightarrow{H^+}$
4. $CH_3C(CH_3){=}CH_2 + CH_3OH \xrightarrow{H^+}$

an ether

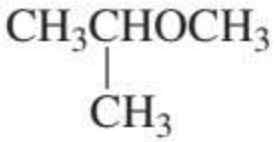
Starting with an alkene, indicate how each of the following compounds can be synthesized:

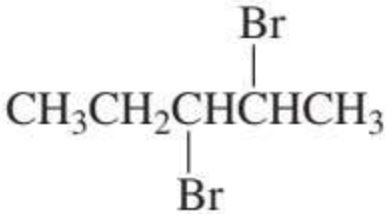
a. 

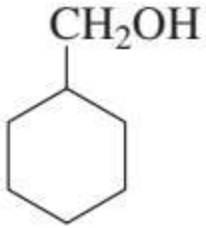
b. 

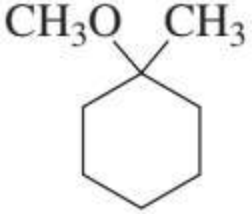
c. 

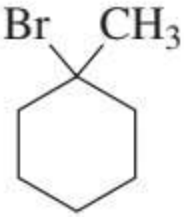
Starting with an alkene, indicate how each of the following compounds can be synthesized:

a. 

b. 

c. 

d. 

e. 

f.